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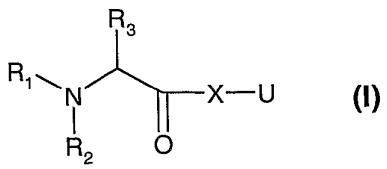
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(54) Title: ORGANIC COMPOUNDS



(I)

(57) Abstract: The present disclosure relates to XIAP inhibitor compounds of the formula (I)

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ORGANIC COMPOUNDS

Summary

The present invention relates generally to novel compounds that inhibit the binding of the Smac protein to Inhibitor of Apoptosis Proteins (IAPs). The present invention includes novel compounds, novel compositions, methods of their use and methods of their manufacture, wherein such compounds are generally pharmacologically useful as agents in therapies whose mechanism of action rely on the inhibition of the IAP/Caspase 9 or Smac/IAP interaction, and more particularly useful in therapies for the treatment of proliferative diseases, including cancer.

Background

Programmed cell death plays a critical role in regulating cell number and in eliminating stressed or damaged cells from normal tissues. Indeed, the network of apoptotic signaling mechanisms inherent in most cell types provides a major barrier to the development and progression of human cancer. Since most commonly used radiation and chemotherapies rely on activation of apoptotic pathways to kill cancer cells, tumor cells which are capable of evading programmed cell death often become resistant to treatment.

Apoptosis signaling networks are classified as either extrinsic when mediated by death receptor-ligand interactions or intrinsic when mediated by cellular stress and mitochondrial permeabilization. Both pathways ultimately converge on individual Caspases. Once activated, Caspases cleave a number of cell death-related substrates, effecting destruction of the cell.

Tumor cells have devised a number of strategies to circumvent apoptosis. One recently reported molecular mechanism involves the over expression of members of the IAP family. IAPs sabotage apoptosis by directly interacting with and neutralizing Caspases. The prototype IAPs, XIAP and cIAP have three functional domains referred to as BIR 1, 2 & 3 domains. BIR3 domain interacts directly with Caspase 9 and inhibits its ability to bind and cleave its natural substrate, Procaspase 3.

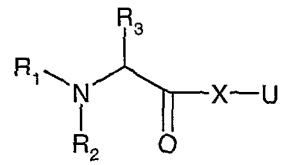
It has been reported that a proapoptotic mitochondrial protein, Smac (also known as DIABLO), is capable of neutralizing XIAP and/or cIAP by binding to a peptide binding pocket (Smac binding site) on the surface of BIR3 thereby precluding interaction between XIAP and/or cIAP and Caspase 9. The present invention relates to therapeutic molecules that bind to the Smac binding pocket thereby promoting Caspase activation. Such therapeutic molecules are useful for the treatment of proliferative diseases, including cancer.

Summary of the Invention

The present invention relates generally to novel compounds that mimic the binding of the Smac protein to Inhibitor of Apoptosis Proteins (IAPs). The present invention includes novel compounds, novel compositions, methods of their use and methods of their manufacture, where such compounds are generally pharmacologically useful as agents in therapies whose mechanism of action rely on the inhibition of the IAP/Caspase 9 or Smac/IAP interaction, and more particularly useful in therapies for the treatment of proliferative diseases, including cancer.

Detailed Description

The present invention relates to compounds of the formula (I)



(I)

wherein

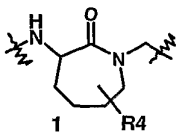
R_1 is H or C_1-C_4 alkyl;

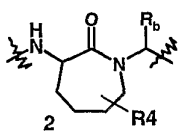
R_2 is H, or C_1-C_4 alkyl which is unsubstituted or substituted by one or more substituents selected from halogen, -OH, -SH, $-OCH_3$, $-SCH_3$, -CN, -SCN and nitro;

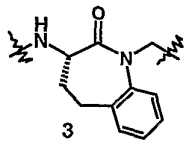
R_3 is H, C_1-C_4 alkyl, $-CF_3$, $-C_2F_5$, $-CH_2$-Z or R_2 and R_3 together form with the nitrogen form a C_3-C_6heteroaliphatic ring;

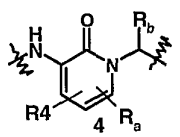
Z is H, -OH, F, Cl, $-CH_3$; $-CF_3$, $-CH_2Cl$, $-CH_2F$ or $-CH_2OH$;

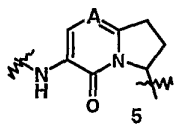
X is a monocyclic or a bicyclic structure selected from the group consisting of:

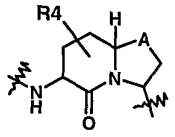

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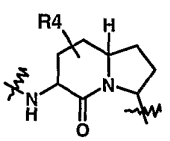

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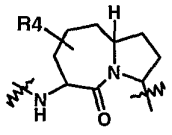

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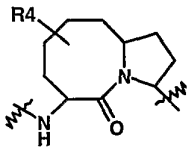

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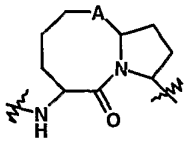

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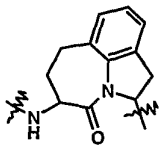

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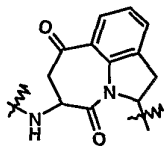

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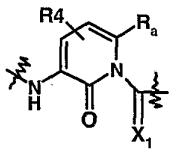

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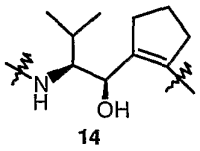

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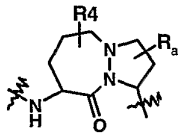

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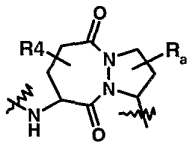

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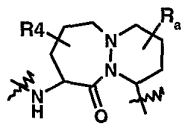

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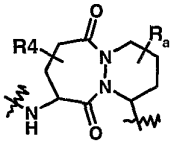

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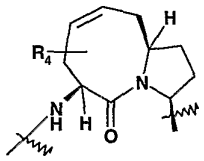

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where

A is -CH_2, -CH-, N, O, or S;

X_1 = O, S, or NR_a;

R_4, R_a and R_b are independently, H; C_1-C_{16} straight or branched alkyl; C_1-C_{16} alkenyl; C_1-C_{16} alkynyl; or C_1-C_{16} cycloalkyl; -$(CH_2)_{0-6}$-phenyl; $(CH_2)_{0-6}$-het; -O-C_1-C_{16} straight or branched alkyl, -S-C_1-C_{16} straight or branched alkyl; -N-C_1-C_{16} straight or branched alkyl; -O-C_1-C_{16} alkenyl; -S-C_1-C_{16} alkenyl; -N-C_1-C_{16} alkenyl -O-C_1-C_{16} cycloalkyl; -N-C_1-C_{16} cycloalkyl; -S-C_1-C_{16} cycloalkyl; -O-$(CH_2)_{0-6}$-phenyl; -N-$(CH_2)_{0-6}$-phenyl; -S-$(CH_2)_{0-6}$-phenyl; -O-$(CH_2)_{0-6}$-het; -N-$(CH_2)_{0-6}$-het and -S-$(CH_2)_{0-6}$-het wherein alkyl, cycloalkyl and phenyl are unsubstituted or substituted; or R_4 and R_a may form a ring;

U is -R_5; -CH(R_5)(R_6); -CO-N(R_5)(R_6); -CO-O(R_5); -CO-S(R_5); -CS-N(R_5)(R_6); -N(R_5)-CO-N(R_5)(R_6); -C_1-C_5-alkyl-N(R_5)(R_6); -C_1-C_5-alkyl-O(R_6) or -C_1-C_5-alkyl-S(O)$_n$(R_6) where n is 0, 1 or 2;

R_5 is H; C_1-C_{10}-alkyl; C_3-C_7-cycloalkyl; -$(CH_2)_{1-6}$-C_3-C_7cycloalkyl; -C_1-C_{10}alkyl-aryl; -$(CH_2)_{0-6}$-phenyl; -$(CH_2)_{0-6}$-C_3-C_7cycloalkyl-$(CH_2)_{0-6}$-phenyl; -$(CH_2)_{0-4}$CH-$((CH_2)_{1-4}$-phenyl$)_2$; -$(CH_2)_{0-6}$-CH(phenyl)$_2$; -C(O)-C_1-C_{10}alkyl; -C(O)-$(CH_2)_{1-6}$-C_3-C_7cycloalkyl; -C(O)-$(CH_2)_{0-6}$-phenyl; -$(CH_2)_{1-6}$-het; -C(O)-$(CH_2)_{1-6}$-het; -$(CR_7R_8)_{0-2}$-Aryl-V-Aryl; $CHR_6C(O)N(R_{12})(R_{13})$; C(O)-NH-$CH(R_{11})(R_{14})$ or R_5 is a residue of an amino acid, wherein the alkyl, cycloalkyl, phenyl and aryl substituents are unsubstituted or substituted;

or when U is -CO-$N(R_5)(R_6)$; -CS-$N(R_5)(R_6)$; -$N(R_5)$-CO-$N(R_5)(R_6)$; or $N(R_5)$-CO-$N(R_5)(R_6)$, R_5 and R_6 together with the N atom form an aromatic or aliphatic heterocycle;

R_7 and R_8 are independently H, halogen; C_{1-7} alkyl; -OC_{1-7} alkyl; C_{1-7} cycloalkyl; or -OC_{1-7} cycloalkyl wherein the alkyl, cycloalkyl substituents may be substituted or unsubstituted;

V is R_9; R_{10}; CR_9R_{10}; -C(O)-; C(hal)$_2$; -O-; -N(H)-; N(alkyl); N(aryl); S; SO; or S(O)$_2$;

R_9 and R_{10} are independently H, halogen, C_{1-7} alkyl;-OC_{1-7} alkyl; C_{1-7} cycloalkyl; or -OC_{1-7} cycloalkyl wherein the alkyl, cycloalkyl substituents may be substituted or unsubstituted;

R_6 is H; -C_1-C_{10} alkyl; -OH; -O-C_1-C_{10}-alkyl; -$(CH_2)_{0-6}$-C_3-C_7-cycloalkyl; -O-$(CH_2)_{0-6}$-aryl; -$(CH_2)_{0-6}$-aryl; phenyl; -$(CH_2)_{1-6}$-het; -O-$(CH_2)_{1-6}$-het; –$N(R_{12})(R_{13})$; -$CNOR_{12}$; -S-R_{12}; -S(O)-R_{12}; -S(O)$_2$-R_{12}; or -S(O)$_2$-$NR_{12}R_{13}$ wherein the alkyl, cycloalkyl and aryl substituents are unsubstituted or substituted;

R_{12} and R_{13} are independently H; C_1-C_{10} alkyl; -$(CH_2)_{0-6}$-C_3-C_7-cycloalkyl; -$(CH_2)_{0-6}$-$(CH)_{0-1}$(aryl)$_{1-2}$; -C(O)-C_1-C_{10}alkyl; -C(O)-$(CH_2)_{1-6}$-C_3-C_7-cycloalkyl; -C(O)-O-$(CH_2)_{0-6}$-aryl; -C(O)-$(CH_2)_{0-6}$-O-fluorenyl; -C(O)-NH-$(CH_2)_{0-6}$-aryl; -C(O)-$(CH_2)_{0-6}$-aryl; or -C(O)-$(CH_2)_{1-6}$-het, wherein the alkyl, cycloalkyl and aryl substituents are unsubstituted or substituted; or a substituent that facilitates transport of the molecule across a cell membrane, or R_{12} and R_{13} together with the nitrogen form an aromatic or aliphatic heterocycle;

where R_{11} and R_{14} are C_{1-7} alkyl; -$(CH_2)_{0-6}$-phenyl; or amide;

aryl is phenyl, naphthyl, or indanyl which is unsubstituted or substituted;

and wherein

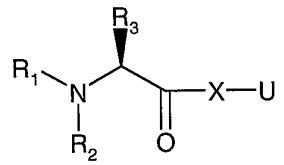
alkyl substituents may be substituted by one or more substituents selected from a double bond, halogen (hal), OH, SH, -O-C_1-C_6alkyl especially -OCH_3, -S-C_1-C_6 alkyl especially -SCH_3, -CN, -SCN, nitro, -$N(R_1)(R_2)$ and -CF_3; alkyl as used in this application includes heteroalkyl wherein one of the carbon atoms in the alkyl chain is substituted with N, O or S;

cycloalkyl substituents may be substituted by one or more substituents selected from a double bond, C_1-C_6 alkyl, halogen, OH, SH, -O-C_1-C_6 alkyl especially -OCH_3, -S-C_1-C_6 alkyl especially -SCH_3, -CN, -SCN, nitro and -CF_3; and

substituted phenyl or aryl are substituted by one or more substituents selected from halogen, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, -CN, -O-C(O)-C_1-C_4 alkyl (substituted or unsubstituted) and -C(O)-O-C_1-C_4 alkyl (substituted or unsubstituted); and pharmaceutically acceptable salts thereof.

The present invention also relates to a method of treating a proliferative disease comprising administering a compound of the formula (I) to a warm-blooded animal, especially a human, and the use of a compound of the formula (I), especially for treating a proliferative disease. The present invention also relates to pharmaceutical preparations comprising a compound of the formula (I), especially for the treatment of a proliferative disease, a process for the manufacture of a compound of the formula (I), and novel starting materials and intermediates for their manufacture. The present invention also relates to the use of a compound of formula (I) in the manufacture of a pharmaceutical preparation for the treatment of a proliferative disease.

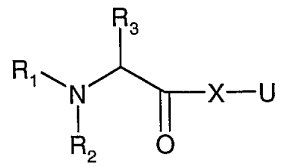
In a particularly important embodiment of the present invention, R_3 has the stereochemistry indicated in formula (II), with the definitions of the variable substituents and preferences described herein also applying to compounds having the stereochemistry indicated in formula (II).



(II)

Preferred Embodiments

One embodiment of the present invention comprises a compound of formula (I):



(I)

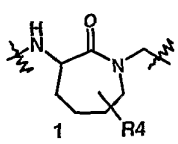
wherein

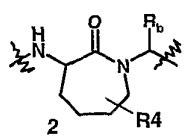
R_1 is H or C_1-C_4 alkyl;

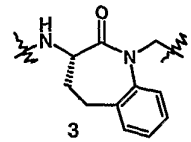
R_2 is H or C_1-C_4 alkyl;

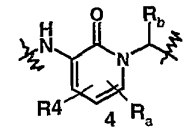
R_3 is H or C_1-C_4 alkyl;

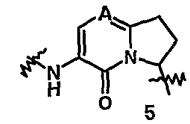
X is a monocyclic or a bicyclic structure selected from the group consisting of:

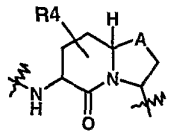

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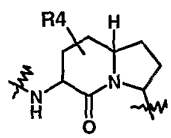

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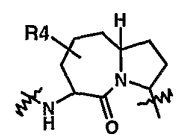

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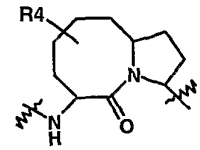

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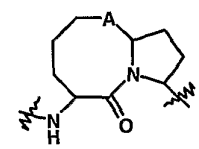

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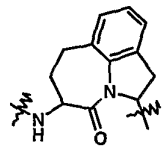

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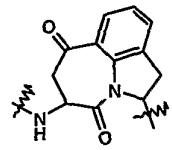

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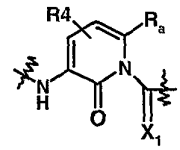

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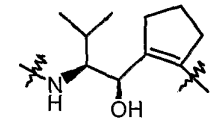

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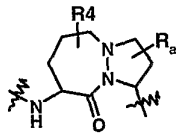

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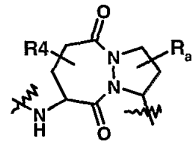

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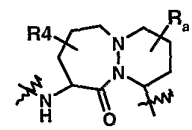

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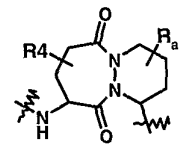

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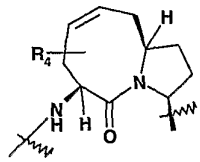

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where

A is -CH_2, -CH-, N, O, or S;

X_1 is O, S, or NR_a;

R_4, R_a and R_b are independently, H; C_1-C_{16} straight or branched alkyl or -$(CH_2)_{0-6}$-phenyl, wherein said phenyl may be unsubstituted or substituted, preferably with halo;

U is -R_5; -$CH(R_5)(R_6)$; or -CO-$N(R_5)(R_6)$;

R_5 is H; C_1-C_{10}-alkyl; -$(CH_2)_{0-6}$-phenyl; -$C(O)$-C_1-C_{10}alkyl; -$C(O)$-$(CH_2)_{0-6}$-phenyl; -$(CR_7R_8)_{0-2}$-Aryl-V-Aryl; $CHR_6C(O)N(R_{12})(R_{13})$; or $C(O)$-NH-$CH(R_{11})(R_{14})$;

R_7 and R_8 are independently H, halogen; C_{1-7} alkyl; -OC_{1-7} alkyl; C_{1-7} cycloalkyl; or -OC_{1-7} cycloalkyl;

V is -$C(O)$-; $C(hal)_2$; -O-; -N(H)-; N(alkyl); N(aryl); S; SO; or $S(O)_2$;

R_9 and R_{10} are independently H, halogen, C_{1-7} alkyl;-OC_{1-7} alkyl; C_{1-7} cycloalkyl; or -OC_{1-7} cycloalkyl;

R_6 is H; -C_1-C_{10} alkyl; -OH; -O-C_1-C_{10}-alkyl; -$(CH_2)_{0-6}$-phenyl; -$(CH_2)_{0-6}$-aryl; -O-$(CH_2)_{0-6}$-aryl; phenyl; -$(CH_2)_{1-6}$-het; -O-$(CH_2)_{1-6}$-het; –$N(R_{12})(R_{13})$; -$CNOR_{12}$; -S-R_{12}; -S(O)-R_{12}; -$S(O)_2$-R_{12}; or -$S(O)_2$-$NR_{12}R_{13}$;

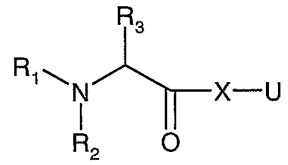
R_{12} and R_{13} are independently H; or C_1-C_{10} alkyl;

where R_{11} and R_{14} are C_{1-7} alkyl; -$(CH_2)_{0-6}$-phenyl; or amide;

aryl is phenyl, naphthyl, or indanyl which is unsubstituted or substituted;

and pharmaceutically acceptable salts thereof.

In an especially preferred embodiment is a compound of formula (I):

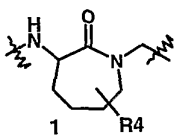


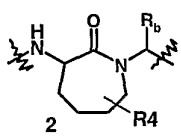
(I)

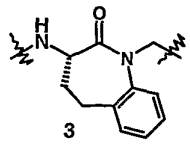
wherein

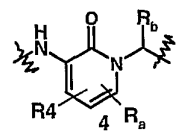
R_1, R_2 and R_3 are independently H or C_1-C_4 alkyl;

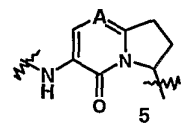
X is a monocyclic or a bicyclic structure selected from the group consisting of:

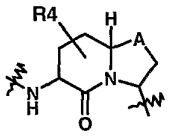

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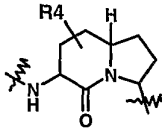

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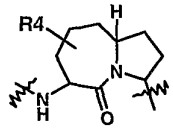

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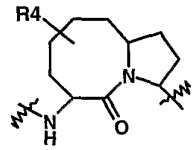

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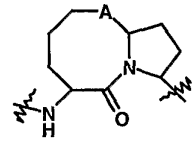

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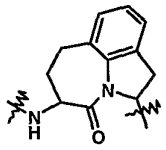

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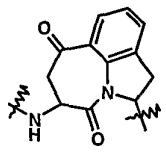

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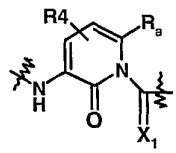

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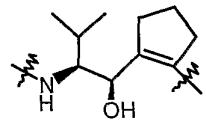

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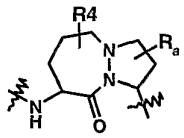

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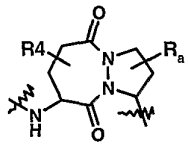

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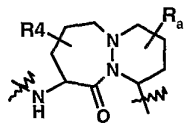

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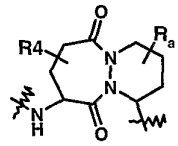

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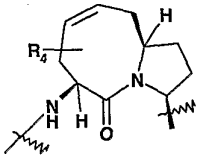

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where

A is -CH_2, -CH-, N, O, or S;

X_1 is O, S, or NR_a;

R_4, R_a and R_b are independently, H; C_1-C_{16} straight or branched alkyl; or -$(CH_2)_{0-6}$-phenyl;

U is -R_5; C_1-C_5alkyl-N(R_5)(R_6); or -CO-N(R_5)(R_6);

R_5 is H; -$(CH_2)_{0-6}$-phenyl; C_1-C_3alkyl; -Aryl-V-Aryl-; or -C(O)-NH-CH(R_{11})(R_{14}) wherein aryl or phenyl may be unsubstituted or substituted, preferably with halo;

V is -O-;

R_6 is H; -C_1-C_{10} alkyl; -OH; -O-C_1-C_{10}-alkyl; -O-$(CH_2)_{0-6}$-phenyl; -$(CH_2)_{0-6}$-phenyl; indanyl; or phenyl;

where R_{11} and R_{14} are C_{1-7} alkyl; -$(CH_2)_{0-6}$-phenyl; or amide;

aryl is phenyl, naphthyl, or indanyl which is unsubstituted or substituted;

and pharmaceutically acceptable salts thereof.

In other preferred embodiment of the present invention compound of formula (I) has the following:

R_1 is H or alkyl.

R_2 is especially H, methyl or ethyl, particularly H or methyl, which methyl group is unsubstituted or substituted, particularly unsubstituted methyl. R_2 as substituted methyl especially includes chloromethyl, dichloromethyl and especially trifluoromethyl.

R_3 is especially methyl or ethyl.

In a particular embodiment, R_2 and R_3 together with the nitrogen form a heteroaliphatic ring, including saturated and unsaturated 3 to 6 membered nonaromatic rings, for example, aziridine, azetidine, azole, piperidine, piperazine, and the like, especially aziridine and azetidine.

R_4 is preferably H, Me, n-Bu, benzyl, phenyl or phenyl-substituted halo.

R_a is preferably H, Me, n-Bu, benzyl, phenyl or phenyl-substituted halo.

R_b is preferably H.

R_5 is -$(CH_2)_{0-6}$-C_3-C_7-cycloalkyl-$(CH_2)_{0-6}$-phenyl includes fused cycloalkyl-phenyl rings, such as indanyl, when there are no methylenes between the cycloalkyl and phenyl rings.

R_5 as -$(CH_2)_{0-4}$CH-$((CH_2)_{1-4}$-phenyl$)_2$ is especially -CH_2CH_2-phenyl, indanyl;

R_5 as -$(CR_7\ R_8)_{0-2}$Aryl-V-Aryl is especially -(CH_2)-Ph-O-Ph or -Ph-O-Ph; Ph-C(O)-Ph; Ph-NH-Ph; Ph-N(Me)-Ph; Ph-S-Ph, Ph-SO_2-Ph; Ph-SO-Ph may be unsubstituted or substituted, preferably with halo.

R_6 is especially H.

A particularly important embodiment includes the compounds wherein R_5 is -C_1-C_4 alkyl-phenyl, especially those wherein R_5 is -C_2H_4-phenyl and R_6 is H.

In a particular embodiment of the present invention, one or both of R_7 and R_8 is H. If one of R_7 and R_8 is other than H, it is especially hydroxy, -$N(R_{12})(R_{13})$, especially wherein R_{12} is -C(O)-$(CH_2)_{1-6}$-C_3-C_7-cycloalkyl, for example, wherein $(CH_2)_{1-6}$-C_3-C_7-cycloalkyl is

cyclohexylmethyl, -O-$(CH_2)_{0-6}$-aryl, for example, wherein $(CH_2)_{0-6}$-aryl is benzyl. If only one of R_7 and R_8 is other than H, it is preferred for R_8 to be the substituent other than H.

In a preferred embodiment, R_6 is H and R_5 is -C_1-C_{10} alkyl-aryl, particularly phenylmethyl, phenylethyl and phenylpropyl, indonyl especially phenylethyl and indanyl.

The general terms used hereinbefore and hereinafter preferably have, within this disclosure, the following meanings, unless otherwise indicated:

Unsubstituted is intended to mean that hydrogen is the only substituent.

Halogen is fluorine, chlorine, bromine or iodine, especially fluorine and chlorine. Unless otherwise specified alkyl substituents include straight or branched chain alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl and branched pentyl, n-hexyl and branched hexyl, and the like.

Cycloalkyl substituents include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

The het substituents include aromatic and non-aromatic heterocyclic rings and fused rings containing aromatic and non-aromatic heterocyclic rings. Suitable het substituents include unsubstituted and substituted pyrrolidyl, tetrahydrofuryl, tetrahydrothiofuranyl, piperidyl, piperazyl, tetrahydropyranyl, morphilino, 1,3-diazapane, 1,4-diazapane, 1,4-oxazepane, 1,4-oxathiapane, furyl, thienyl, pyrrole, pyrazole, triazole, tetrazole, thiazole, oxazole, pyridine, pyrimidine, isoxazolyl, pyrazine, quinoline, isoquinoline, pyridopyrazine, pyrrolopyridine, furopyridine, indole, benzofuran, benzothiofuran, benzindole, benzoxazole, pyrroloquinoline, and the like. The het substituents are unsubstituted or substituted on a carbon atom by halogen, especially fluorine or chlorine, hydroxy, C_1-C_4 alkyl, such as methyl and ethyl, C_1-C_4 alkoxy, especially methoxy and ethoxy, nitro, -O-C(O)-C_1-C_4alkyl or -C(O)-O-C_1-C_4-alkyl or on a nitrogen by C_1-C_4 alkyl, especially methyl or ethyl, -O-C(O)-C_1-C_4 alkyl or -C(O)-O-C_1-C_4 alkyl, such as carbomethoxy or carboethoxy.

When two substituents together with a commonly bound nitrogen are het, it is understood that the resulting heterocyclic ring is a nitrogen-containing ring, such as aziridine, azetidine, azole, piperidine, piperazine, morphiline, pyrrole, pyrazole, thiazole, oxazole, pyridine, pyrimidine, isoxazolyl, and the like.

Substituents that facilitate transport of the molecule across a cell membrane are known to those of skill in the medicinal chemistry arts (see, for example, Gangewar S., Pauletti G.M., Wang B., Siahaan T.J., Stella V.J., Borchardt R.T., *Drug Discovery Today*, vol. 2, p 148-155 (1997) and Bundgaard H. and Moss J., *Pharmaceutical Research*, vol. 7, p 885 (1990)). Generally, such substituents are lipophillic substituents. Such lipophillic substituents include a C_6-C_{30} alkyl which is saturated, monounsaturated, polyunsaturated, including methylene-interrupted polyene, phenyl, phenyl which substituted by one or two C_1-C_8 alkyl groups, C_5-C_9 cycloalkyl, C_5-C_9 cycloalkyl which is substituted by one or two C_1-C_8 alkyl groups, -X_1-phenyl, -X_1-phenyl which is substituted in the phenyl ring by one or two C_1-C_8 alkyl groups, X_1-C_5-C_9 cycloalkyl or X_1-C_5-C_9 cycloalkyl which is substituted by one or two C_1-C_8 alkyl groups; where X_1 is C_1-C_{24} alkyl which is saturated, monounsaturated or polyunsaturated and straight or branched chain.

It will be apparent to one of skill in the art when a compound of the invention can exist as a salt form, especially as an acid addition salt or a base addition salt. When a compound can exist in a salt form, such salt forms are included within the scope of the invention. Although any salt form may be useful in chemical manipulations, such as purification procedures, only pharmaceutically acceptable salts are useful for pharmaceutically products.

Pharmaceutically acceptable salts include, when appropriate, pharmaceutically acceptable base addition salts and acid addition salts, for example, metal salts, such as alkali and alkaline earth metal salts, ammonium salts, organic amine addition salts, and amino acid addition salts, and sulfonate salts. Acid addition salts include inorganic acid addition salts such as hydrochloride, sulfate and phosphate, and organic acid addition salts such as alkyl sulfonate, arylsulfonate, acetate, maleate, fumarate, tartrate, citrate and lactate. Examples of metal salts are alkali metal salts, such as lithium salt, sodium salt and potassium salt, alkaline earth metal salts such as magnesium salt and calcium salt, aluminum salt, and zinc salt. Examples of ammonium salts are ammonium salt and tetramethylammonium salt. Examples of organic amine addition salts are salts with morpholine and piperidine. Examples of amino acid addition salts are salts with glycine, phenylalanine, glutamic acid and lysine. Sulfonate salts include mesylate, tosylate and benzene sulfonic acid salts.

For the purposes of isolation or purification, as well as in the case of compounds that are used further as intermediates, it is also possible to use pharmaceutically unacceptable salts, e.g., the picrates. Only pharmaceutically acceptable, non-toxic salts may be used for therapeutic purposes, however, and those salts are therefore preferred.

Synthetic Procedure

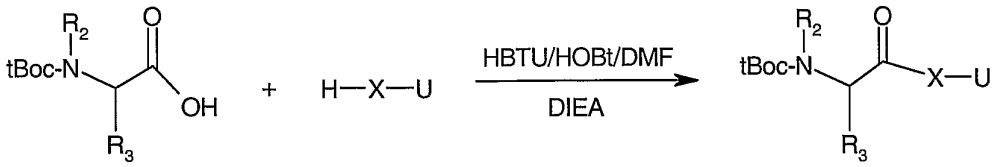
Abbreviations:

CH_2Cl_2	methylene chloride
CH_3CN	acetonitrile
DIBAL	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DME	ethylene glycol dimethyl ether
DMF	*N, N*-dimethylformamide
DTBB	4,4'-di-tert-butylbiphenyl
EtOAc	ethyl acetate
HBTU	*O*-benzyltriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HOBt	1-hydroxhbenzotriazole
HPLC	high performance liquid chromatography
KOTMS	potassium trimethysilanoate.
MeOH	methanol
$MgSO_4$	magnesium sulfate
MnO_2	manganese dioxide
Na_2CO_3	sodium carbonate
$NaHCO_3$	sodium bicarbonate
NaOH	sodium hydroxide
Tetrakis	tetrakis(triphenylphosphine)palladium(0)
TFA	trifluoroacetic acid
THF	tetrahydrofuran

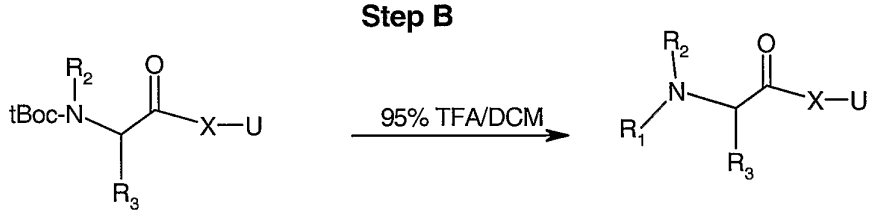
The compounds of formula (I) may be prepared as depicted below in Scheme 1:

Scheme 1

Step A



Step B



$R_1 = H$

Step A: This step involves the coupling of an amine HXU (prepared in this invention or purchased from commercial sources) with a *t*-Boc-L-amino acid or its derivative using standard peptide coupling agents such as DCC/HOBt or HBTU/HOBt.

Step B: This step involves the removal of *t*-Boc group with trifluoroacetic acid (TFA).

As discussed above, the compounds of the present invention are useful for treating proliferative diseases. Thus, the present invention further relates to a method of treating a proliferative disease which comprises administering a therapeutically effective amount of a compound of the invention to a mammal, preferably a human, in need of such treatment.

A proliferative disease is mainly a tumor disease (or cancer) (and/or any metastases). The inventive compounds are particularly useful for treating a tumor which is a breast cancer, genitourinary cancer, lung cancer, gastrointestinal cancer, epidermoid cancer, melanoma, ovarian cancer, pancreas cancer, neuroblastoma, head and/or neck cancer or bladder cancer, or in a broader sense renal, brain or gastric cancer; in particular,

(i) a breast tumor; an epidermoid tumor, such as an epidermoid head and/or neck tumor or a mouth tumor; a lung tumor, for example, a small cell or non-small cell lung tumor; a gastrointestinal tumor, for example, a colorectal tumor; or a genitourinary

tumor, for example, a prostate tumor (especially a hormone-refractory prostate tumor); or

(ii) a proliferative disease that is refractory to the treatment with other chemotherapeutics; or

(iii) a tumor that is refractory to treatment with other chemotherapeutics due to multi-drug resistance.

In a broader sense of the invention, a proliferative disease may furthermore be a hyperproliferative condition such as leukemias, hyperplasias, fibrosis (especially pulmonary, but also other types of fibrosis, such as renal fibrosis), angiogenesis, psoriasis, atherosclerosis and smooth muscle proliferation in the blood vessels, such as stenosis or restenosis following angioplasty.

Where a tumor, a tumor disease, a carcinoma or a cancer are mentioned, also metastasis in the original organ or tissue and/or in any other location are implied alternatively or in addition, whatever the location of the tumor and/or metastasis.

The inventive compound is selectively toxic or more toxic to rapidly proliferating cells than to normal cells, particularly in human cancer cells, e.g., cancerous tumors, the compound has significant antiproliferative effects and promotes differentiation, e.g., cell cycle arrest and apoptosis.

The present invention further relates to a method of promoting apoptosis in rapidly proliferating cells, which comprises contacting the rapidly proliferating cells with an effective apoptosis promoting amount of a non-naturally-occurring compound that binds to the Smac binding site of XIAP and/or cIAP proteins. Preferably, the non-naturally-occurring compound a compound of present formula (I) or (II).

Pharmaceutical Compositions

The invention relates also to pharmaceutical compositions comprising a compound of formula (I), to their use in the therapeutic (in a broader aspect of the invention also prophylactic) treatment or a method of treatment of a kinase dependent disease, especially the preferred diseases mentioned above, to the compounds for said use and to pharmaceutical preparations and their manufacture, especially for said uses.

The present invention also relates to pro-drugs of a compound of formula (I) that convert *in vivo* to the compound of formula (I) as such. Any reference to a compound of formula (I) is therefore to be understood as referring also to the corresponding pro-drugs of the compound of formula (I), as appropriate and expedient.

The pharmacologically acceptable compounds of the present invention may be present in or employed, for example, for the preparation of pharmaceutical compositions that comprise an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as active ingredient together or in admixture with one or more inorganic or organic, solid or liquid, pharmaceutically acceptable carriers (carrier materials).

The invention relates also to a pharmaceutical composition that is suitable for administration to a warm-blooded animal, especially a human (or to cells or cell lines derived from a warm-blooded animal, especially a human, e.g., lymphocytes), for the treatment of (this, in a broader aspect of the invention, also includes the prevention of (= prophylaxis against)) a disease that responds to inhibition of protein kinase activity, comprising an amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, preferably which is effective for said inhibition, together with at least one pharmaceutically acceptable carrier.

The pharmaceutical compositions according to the invention are those for enteral, such as nasal, rectal or oral, or parenteral, such as intramuscular or intravenous, administration to warm-blooded animals (especially a human), that comprise an effective dose of the pharmacologically active ingredient, alone or together with a significant amount of a pharmaceutically acceptable carrier. The dose of the active ingredient depends on the species of warm-blooded animal, the body weight, the age and the individual condition, individual pharmacokinetic data, the disease to be treated and the mode of administration.

The invention relates also to a method of treatment for a disease that responds to inhibition of a protein kinase and/or a proliferative disease, which comprises administering a (against the mentioned diseases) prophylactically or especially therapeutically effective amount of a compound of formula (I) according to the invention, or a tautomer thereof or a pharmaceutically acceptable salt thereof, especially to a warm-blooded animal, for example, a human, that, on account of one of the mentioned diseases, requires such treatment.

The dose of a compound of the formula (I) or a pharmaceutically acceptable salt thereof to be administered to warm-blooded animals, for example, humans of approximately 70 kg body weight, preferably is from approximately 3 mg to approximately 10 g, more preferably from approximately 10 mg to approximately 1.5 g, most preferably from about 100 mg to about 1,000 mg/person/day, divided preferably into 1-3 single doses which may, for example, be of the same size. Usually, children receive half of the adult dose.

The pharmaceutical compositions comprise from approximately 1% to approximately 95%, preferably from approximately 20% to approximately 90%, active ingredient. Pharmaceutical compositions according to the invention may be, for example, in unit dose form, such as in the form of ampoules, vials, suppositories, dragées, tablets or capsules.

The pharmaceutical compositions of the present invention are prepared in a manner known *per se*, for example, by means of conventional dissolving, lyophilizing, mixing, granulating or confectioning processes.

Examples

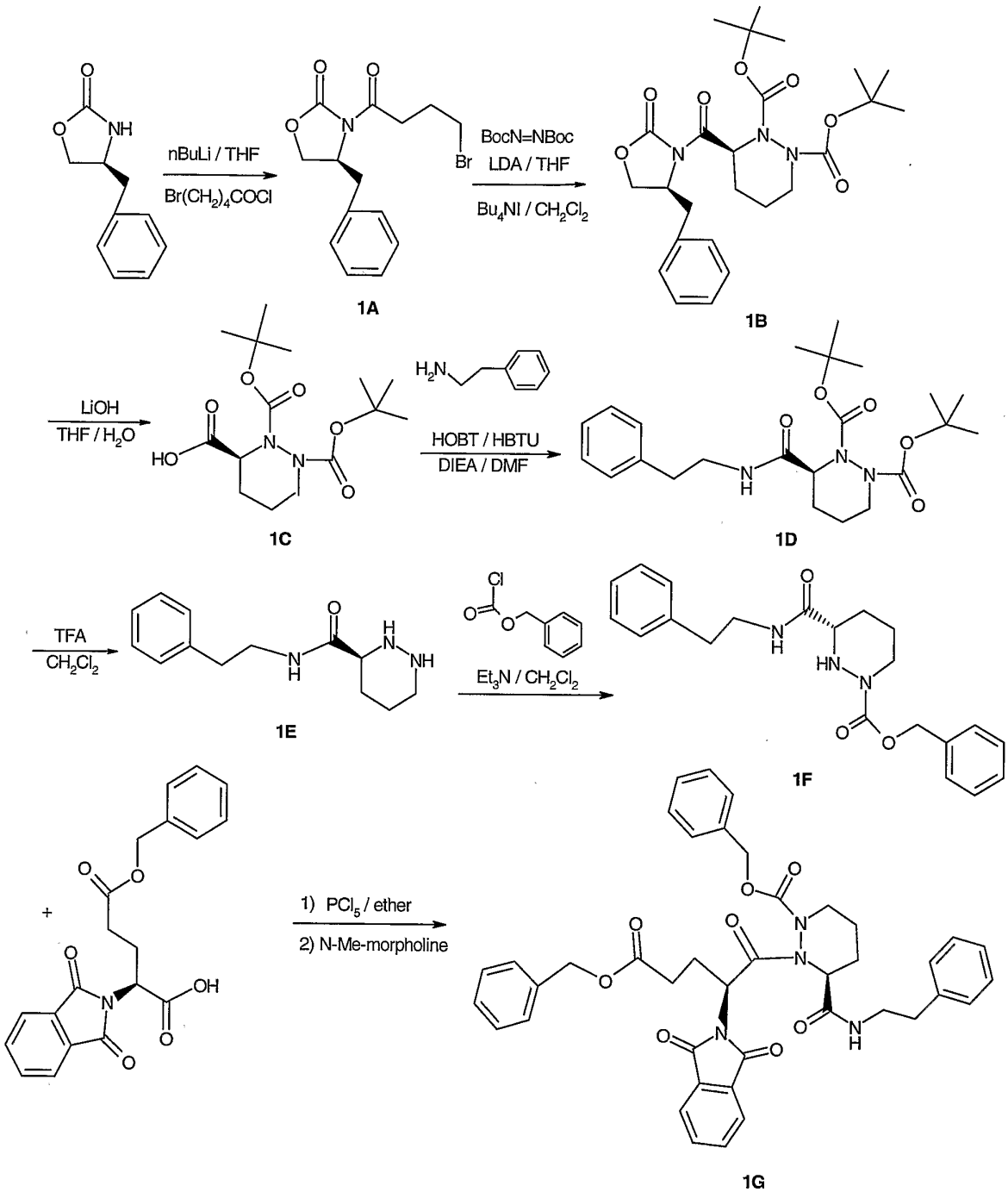
The following Examples serve to illustrate the invention without limiting the scope thereof.

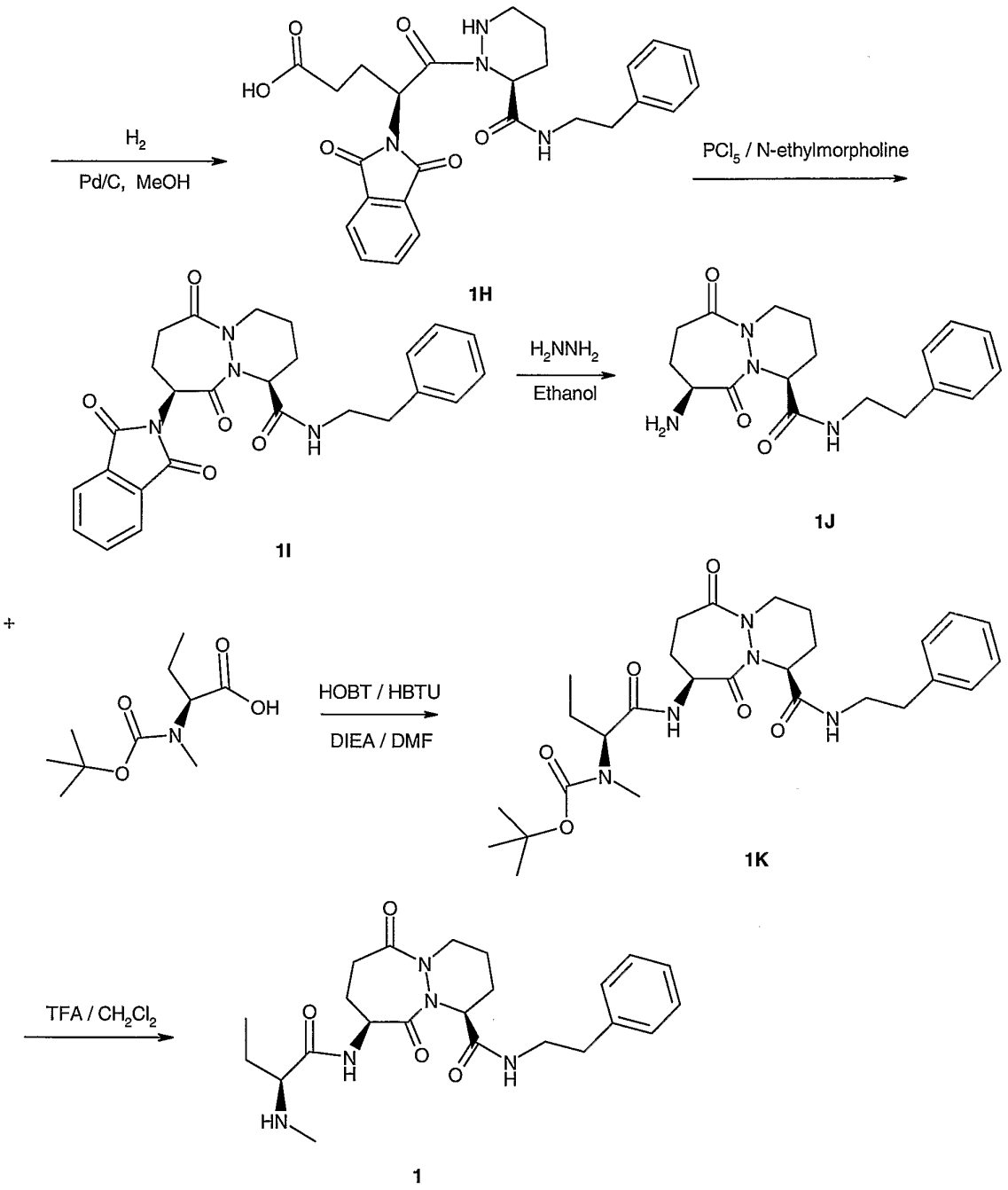
The following examples are intended to illustrate, but not further limit, the invention.

Example 1 **Synthesis of (1S,9S)-9-((S)-2-Methylamino-butyrylamino)-6, 10-dioxo-octahydro-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid phenethyl-amide (1)**

The title compound **1** (formula 1) is prepared according to the procedure set forth in Scheme 2.

Scheme 2


nBuLi / THF
Br(CH2)4COCl
BocN=NBoc
LDA / THF
Bu4NI / CH2Cl2
1A
1B
LiOH
THF / H2O
HOBT / HBTU
DIEA / DMF
1C
1D
TFA
CH2Cl2
Et3N / CH2Cl2
1E
1F
1) PCl5 / ether
2) N-Me-morpholine
1G


H2
Pd/C, MeOH
PCl5 / N-ethylmorpholine
1H
H2NNH2
Ethanol
1I
1J
+
HOBT / HBTU
DIEA / DMF
1K
TFA / CH2Cl2
1

(S)-4-Benzyl-3-(4-bromo-butyryl)-oxazolidin-2-one (1A)

To a solution of S-(-)-4-benzyl-2-oxazolidinone (8.0 g, 45.1mmol) in THF (75 mL) at -70 °C, is added n-BuLi (19.8 mL, 49.6 mmol, 2.5 M in hexane) slowly. After stirring at -70 °C for 1 hour, 5-bromovaleryl chloride (11.7 g, 58.7 mmol) is added dropwise. After stirring at -70 °C for 20 minutes, the cooling bath is removed and the reaction mixture is warmed to 25 °C and stirred for 2 hours. The solution is diluted with 150 mL of ether, and washed with 2 x 100 mL of water. The combined organic layers is dried over Na_2SO_4 and concentrated. The crude product is purified by chromatography (hexane/EtOAc:85/15) to give a white solid (15.3 g, 99.7%). (NMR and MS data confirmed, U-3133-51-24).

(S)-3-((S)-4-Benzyl-2-oxo-oxazolidine-3-carbonyl)-tetrahydro-pyridazine-1,2-dicarboxylic acid di-tert-butyl ester (1B)

To a solution of diisopropylamine (0.77 mL, 5.53 mmol) in THF(4 mL) at 0 °C is added BuLi (2.17 mL, 5.42 mmol, 2.5 M in hexane) dropwise. The solution is stirred at 0 °C for 30 minutes to form an LDA solution. The LDA solution is cold to -70 °C and added to a solution of (S)-4-benzyl-3-(4-bromo-butyryl)-oxazolidin-2-one (1.72 g, 5.07 mmol) in THF (4 mL) at -70 °C dropwise. After stirring at -70 °C for 2 hours, a solution of di-t-butyl azodicarboxylate (1.40 g, 6.08 mmol) in CH_2Cl_2 (4mL) is added slowly. After stirring at -70 °C for 15 minutes, Bu_4NI (0.28 g, 0.76 mmol) is added in one portion. After stirring at -70 °C for 10 minutes, the flask with reaction mixture is moved to a -20 °C bath and stirred overnight (16 hours). The reaction mixture is quenched to ether (50 mL) with buffer solution (50 mL, Ph = 7), and the mixture is extracted with ether (3 x 50 mL). The organic layer is dried over Na_2SO_4 and concentrated. The crude product is purified by chromatography (hexane/EtOAc:70/30) to give (S)-3-((S)-4-benzyl-2-oxo-oxazolidine-3-carbonyl)-tetrahydro-pyridazine-1,2-dicarboxylic acid di-tert-butyl ester as white solid (1.22 g, 49.3%). (NMR and MS data confirmed, U-3133-55-30).

(S)-Tetrahydro-pyridazine-1,2,3-tricarboxylic acid 1,2-di-tert-butyl ester (1C)

To a solution of (S)-3-((S)-4-benzyl-2-oxo-oxazolidine-3-carbonyl)-tetrahydro-pyridazine-1,2-dicarboxylic acid di-tert-butyl ester (1.22 g, 2.5 mmol) in THF (15 mL) at 0 °C, is added a solution of LiOH (7 mL, 5% in H_2O). After stirring at 0 °C for 2 hours, the reaction mixture is diluted with 15 mL of water and extracted with 20 mL of ether. The ether layer is extracted with 10 mL of saturated $NaHCO_3$. The combined aqueous layers is acidified with saturated $NaHSO_4$ to Ph = 2, and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers is

dried over Na_2SO_4 and concentrated to give clued product (0.83 g) as a pale gum without further purification for next step reaction. (NMR and MS data confirmed, U-3133-56-22).

(S)-3-Phenethylcarbamoyl-tetrahydro-pyridazine-1,2-dicarboxylic acid di-tert-butyl ester (1D)

To a solution of (S)-tetrahydro-pyridazine-1,2,3-tricarboxylic acid 1,2-di-tert-butyl ester (83 mg, 2.5 mmol) in DMF(10 mL) at room temperature, is added diisopropylethylamine (1.4 mL) slowly. After stirring at room temperature for 20 minutes, to the reaction mixture, is added phenethylamine (445 mg, 3.67 mmol), and followed by a solution of HOBT (545 mg, 4.04 mmol) and HBTU (1.53 g, 4.04 mmol) in DMF(10 mL). After stirring for 1.5 hours at room temperature, the reaction solution is diluted with ether (100 mL), and washed with water(2 x 50 mL). The combined organic solution is concentrated. The crude product is diluted with CH_2Cl_2 and dried over Na_2SO_4, and purified by chromatography (CH_2Cl_2/MeOH:97/3) to give (S)-3-phenethyl carbamoyl-tetrahydro-pyridazine-1,2-dicarboxylic acid di-tert-butyl ester as pale gum (920 mg, 83.6% in two steps). (NMR and MS data confirmed, U-3133-57-26).

(S)-Hexahydro-pyridazine-3-carboxylic acid phenethyl-amide (1E)

To a solution of (S)-3-phenethyl carbamoyl-tetrahydro-pyridazine-1,2-dicarboxylic acid di-tert-butyl ester (920 mg, 2.12 mmol) in CH_2Cl_2 (2 mL) at -20 °C is added TFA (4 mL, pre-cooled to -20 °C) slowly. After stirring at 0 °C for 30 minutes, the reaction mixture is concentrated by rotavaporation under room temperature. The residue is diluted with CH_2Cl_2/H_2O (20 mL, 8/2), and neutralized with 10% NH_4OH to Ph = 7. After dried and concentrated to give crude (S)-hexahydropyridazine-3-carboxylic acid phenethyl-amide (376 mg, 76.4%) as pale gum without further purification for next step reaction. (NMR and MS data confirmed, U-3133-58-18).

(S)-3-Phenethylcarbamoyl-tetrahydro-pyridazine-1-carboxylic acid benzyl ester (1F)

To a solution of (S)-hexahydro pyridazine-3-carboxylic acid phenethyl-amide (376 mg, 1.59 mmol) and Et_3N (0.66 mL) in CH_2Cl_2 (10 mL) at 0 °C, is added benzylchloroformate (270 mg, 1.59 mmol) dropwise. After stirring at -5 °C for 1.5 hours, the reaction mixture is diluted with CH_2Cl_2 (50 mL) and washed with 10 mL of water. The organic layer is dried over Na_2SO_4 and concentrated to give (S)-3-phenethylcarbamoyl-tetrahydro-pyridazine-1-carboxylic acid benzyl ester (580 mg) as pale gum without further purification for next step reaction. (NMR and MS data confirmed, U-3133-59).

(S)-2-[(S)-4-Benzyloxycarbonyl-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyryl]-3-phenethylcarbamoyl-tetrahydro-pyridazine-1-carboxylic acid benzyl ester (1G)

To a solution of (S)-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pentanedioic acid 5-benzyl ester (580 mg, 1.59 mmol) in ether (25 mL) at 0 °C, is added PCl_5 (920 mg, 4.38 mmol) in one portion. After stirring at 25 °C for 40 minutes, ether is removed by evaporation, and the residue is dissolved in 20 mL of THF, and is added to a solution of (S)-3-phenethylcarbamoyl-tetrahydro-pyridazine-1-carboxylic acid benzyl ester (580 mg) and N-methylmorpholine (0.74 mL, 6.77 mmol) in THF (10 mL) at 0 °C slowly. After stirring at room temperature for 2 hours, the reaction mixture is diluted with 100 mL of ether and washed with 2 x 20 mL of water. The combined organic layers is dried over Na_2SO_4 and concentrated, and purified by chromatography (CH_2Cl_2/MeOH:97/3) to give (S)-2-[(S)-4-benzyloxycarbonyl-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyryl]-3-phenethylcarbamoyl-tetrahydro-pyridazine-1-carboxylic acid benzyl ester (1.13 g, 99.2%) as pale solid. (NMR and MS data confirmed, U-3133-62).

(S)-4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-5-oxo-5-((S)-6-phenethylcarbamoyl-tetrahydro-pyridazin-1-yl)-pentanoic acid (1H)

A solution/suspension of (S)-2-[(S)-4-benzyloxycarbonyl-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyryl]-3-phenethylcarbamoyl-tetrahydro-pyridazine-1-carboxylic acid benzyl ester (1.13 g) and Pd/C (350 mg, 10% on carbon) in MeOH (15 mL, with 2 drops of acetic acid) in a 1,000 mL round flask is vigorously stirred at room temperature, under hydrogen gas (at atmosphere pressure) from a balloon for 3 hours. After degassed by house vacuum for 10 minutes, the reaction mixture is filtered to remove catalyst and concentrated. The crude product is diluted with CH_2Cl_2/H_2O (10 mL, 8/2) and neutralized with 10% NH_4OH to Ph = 7. After dried and concentrated, the crude product is purified by chromatography (CH_2Cl_2/MeOH:97/3) to give (S)-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-5-oxo-5-((S)-6-phenethylcarbamoyl-tetrahydro-pyridazin-1-yl)-pentanoic acid (0.74 g, 95.3%) as pale solid. (NMR and MS data confirmed, U-3133-63).

(1S,9S)-9-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-6,10-dioxo-octahydro-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid phenethyl-amide (1I)

To a solution of (S)-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-5-oxo-5-((S)-6-phenethylcarbamoyl-tetrahydro-pyridazin-1-yl)-pentanoic acid (0.74 g, 1.5 mmol) and N-methylmorpholine (0.6 g, 6.0 mmol) in THF (20mL) at 0 °C, is added PCl_5 (470 mg,

2.25 mmol) in one portion. After stirring at 0 °C for 3 hours, the reaction mixture is concentrated and purified by chromatography (CH_2Cl_2/MeOH:97/3) to yield (1S,9S)-9-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-6,10-dioxo-octahydro-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid phenethyl-amide (310 mg, 43.6%) as white solid. (NMR and MS data confirmed, U-3133-65).

(1S,9S)-9-Amino-6,10-dioxo-octahydro-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid phenethyl-amide (1J)

To a mixture/suspension of (1S,9S)-9-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-6,10-dioxo-octahydro-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid phenethyl-amide (310 mg, 0.70 mmol) and hydrozinehydrate (70 mg, 1.40 mmol) in ethanol (10mL) is stirred at 60 °C for 2 hours. After cooled to room temperature and concentrated, the reaction mixture is purified by chromatography (CH_2Cl_2/MeOH:97/3) to give (1S,9S)-9-amino-6,10-dioxo-octahydro-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid phenethyl-amide (240 mg, 99%) as white solid. (NMR and MS data confirmed, U-3133-67).

[(S)-1-((4S,7S)-6,10-Dioxo-4-phenethylcarbamoyl-octahydro-pyridazino[1,2-a][1,2]diazepin-7-ylcarbamoyl)-propyl]-methyl-carbamic acid tert-butyl ester (1K)

To a solution of (S)-2-(tert-butoxycarbonyl-methyl-amino)-butyric acid (167 mg, 0.77 mmol) in DMF (5 mL) at room temperature, is added diisopropylethylamine (0.48 mL) slowly. After stirring at room temperature for 20 minutes, the solution is transferred to another flask contained (1S,9S)-9-amino-6,10-dioxo-octahydro-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid phenethyl-amide (240 mg, 0.70 mmol), and then a solution of HOBT (125 mg, 0.92 mmol) and HBTU (350 mg, 0.92 mmol) in DMF (5 mL) is added to the reaction mixture. After stirring for 1.5 hours, the reaction solution is diluted with ether (20 mL), and washed with water (2 x 10 mL). The combined organic layers is concentrated. The crude product is diluted with CH_2Cl_2 (10 mL) and dried over Na_2SO_4, and purified by chromatography (CH_2Cl_2/MeOH:97/3) to give (S)-1-((4S,7S)-6,10-dioxo-4-phenethylcarbamoyl-octahydro-pyridazino[1,2-a][1,2]diazepin-7-ylcarbamoyl)-propyl]-methyl-carbamic acid tert-butyl ester (270 mg, 71.3%) as pale solid. (NMR and MS data confirmed, U-3133-69).

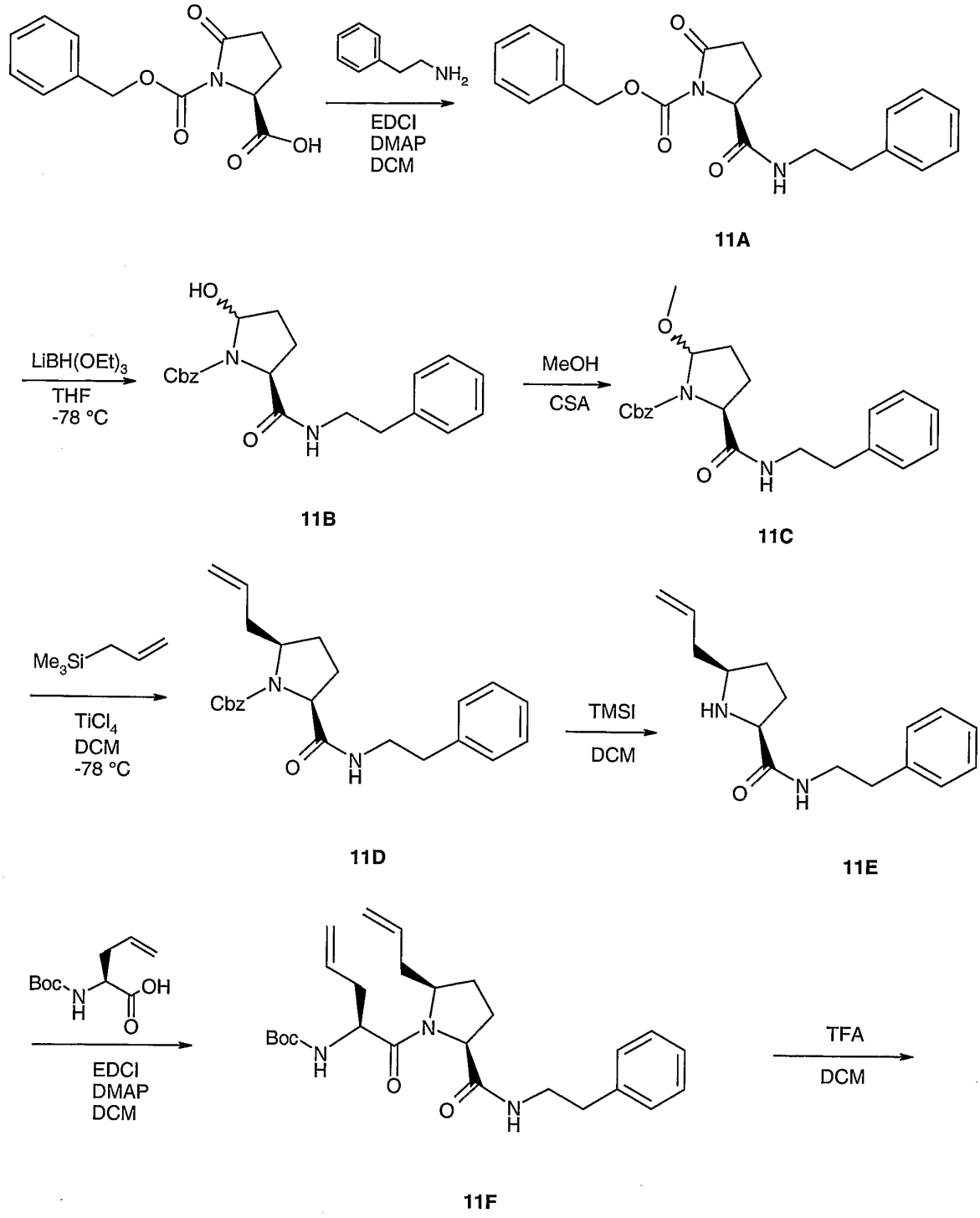
(1S,9S)-9-((S)-2-Methylamino-butyrylamino)-6,10-dioxo-octahydro-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid phenethyl-amide (1)

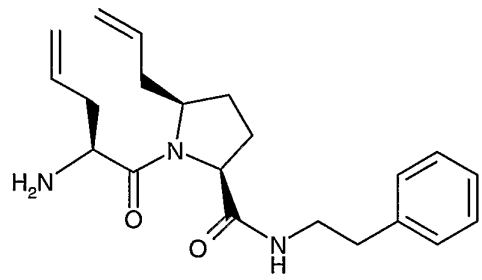
To a solution of (S)-1-((4S,7S)-6,10-dioxo-4-phenethylcarbamoyl- octahydro-pyridazino[1,2-a][1,2]diazepin-7-ylcarbamoyl)-propyl]-methyl-carbamic acid tert-butyl ester (270 mg, 0.50 mmol) in CH_2Cl_2 (1 mL) at -20 °C is added TFA (5 mL, pre-cooled to -20 °C) slowly. After stirring at 0 °C for 30 minutes, the reaction mixture is concentrated and purified by prep HPLC (column: waters prep C18 40 x 300 mm; mobile phase: gradient condition, started at CH_3CN 10%/H_2O 90% with 0.1%TFA, 10 minutes changed lineally to CH_3CN 100% with 0.1% TFA; flow rate: 25 mL/min.) to give(1S,9S)-9-((S)-2-methylamino-butyrylamino)-6,10-dioxo-octahydro-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid phenethyl-amide (230 mg) as TFA salt/white solid. (NMR and MS data confirmed, U-3133-73).

Example 2 Synthesis of (Z)-(2S,5S)-5-ethyl-1-[(S)-2-((S)-2-methylamino-propionylamino)-pentanoyl]-pyrrolidine-2-carboxylic acid phenethyl-amide (11) and (Z)-(3S,6S,10aR)-6-((S)-2-methylamino-propionylamino)-5-oxo-1,2,3,5,6,7,10,10a-octahydro-pyrrolo[1,2-a]azocine-3-carboxylic acid phenethylamide (12)

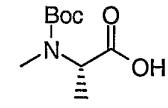
The title compounds **11** and **12** (formula 1) is prepared according to the procedure set forth in Scheme 3:

Scheme 3

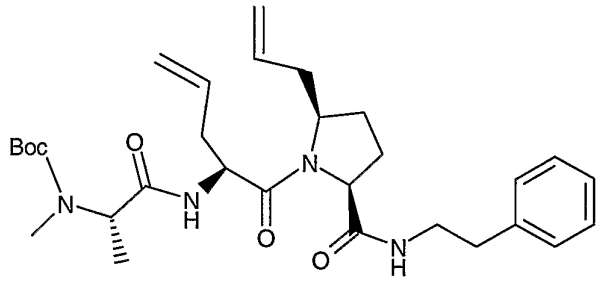

EDCI
DMAP
DCM
11A
LiBH(OEt)3
THF
-78 °C
11B
MeOH
CSA
11C
Me3Si
TiCl4
DCM
-78 °C
11D
TMSI
DCM
11E
EDCI
DMAP
DCM
11F
TFA
DCM



11G

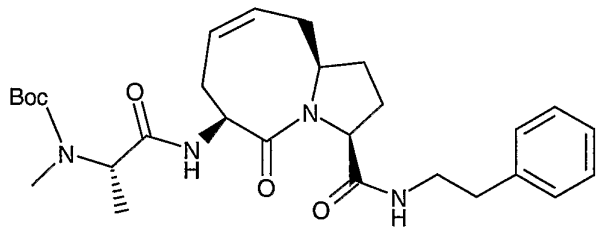


EDCI
DMAP
DCM



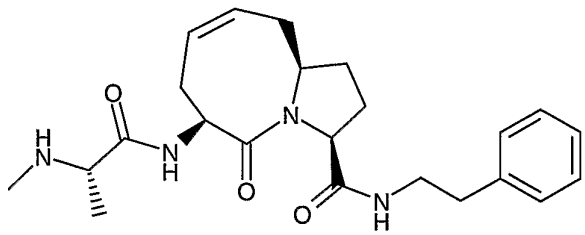
11H

Grubbs II
DCM
50 °C



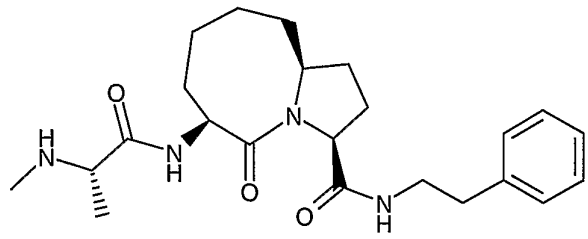
11I

TF
DC



12

H_2
Pd/C



11

(S)-2-Oxo-5-phenethylcarbamoyl-pyrrolidine-1-carboxylic acid benzyl ester (11A)

(S)-5-Oxo-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester (14.9 g, 57 mmol) is suspended in dichloromethane (100 mL) and added DMAP (7.1 g, 58 mmol) while cooling on ice (0-5 °C). The suspension immediately clarified. EDCI (11.1 g, 58 mmol) is added resulting in precipitation which quickly clarified again. Phenethylamine (6.8 mL, 54 mmol) is added slowly via syringe. The reaction is complete in one half hour. The dichloromethane layer is washed with aqueous 10% citric acid, water and saturated bicarb, then dried over anhydrous sodium sulfate, filtered and concentrated to a white solid. LCMS characterization ES+ 367.1 (m+1).

(S)-5-Hydroxy-1-methyl-pyrrolidine-2-carboxylic acid phenethyl-amide (11B)

A THF solution of **11A** pyroglutamide (3.9 g, 11 mmol) is chilled to -78 °C. After 15 minutes, 1 M super-hydride solution (13 mL, 13 mmol) is slowly added. After 1 hour, it is carefully quenched with saturated bicarb and added 4 mL 30% hydrogen peroxide and concentrated to half volume and reconstituted with ethyl acetate, then washed with saturated bicarb and brine and dried over anhydrous sodium sulfate, filtered and concentrated to a clear oil. LCMS characterization ES+ 369.1 (m+1).

(S)-5-Methoxy-1-methyl-pyrrolidine-2-carboxylic acid phenethyl-amide (11C)

Product **11B** is dissolved hemi-aminal in 10 mL anhydrous methanol and 100 mg 10-camphorsulfonic acid is added. Methanolysis is complete in 1 hour. The resulting material is filtered and concentrated, then reconstituted with ethyl acetate and washed with saturated bicarb followed by drying over anhydrous sodium sulfate, filtered and concentrated. LCMS characterization ES+ 383.1 (m+1).

(2S,5R)-5-Allyl-1-methyl-pyrrolidine-2-carboxylic acid phenethyl-amide (11D)

A dichloromethane (20 mL) solution of **11C** methylaminal (7.7 g, 20 mmol) is chilled to -78 °C. After 20 minutes, allyltrimethylsilane (6.5 mL, 40 mmol) is added. After 10 more minutes 1 M titanium(IV) chloride (24 mL, 24 mmol) is added slowly by syringe. The reaction is complete after 1 hour. The resulting material is carefully quenched (frothing) with saturated bicarb and extracted with dichlomethane, then washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The product is isolated by flash chromatography (SiO_2), and it crystallizes upon standing. LCMS characterization ES+ 393.1 (m+1).

(2S,5R)-5-Allyl-pyrrolidine-2-carboxylic acid phenethyl-amide (11E)

Dissolved **11D** Cbz-homoallylproline amide (4.3 g, 11 mmol) in dichloromethane (11 mL, 1 M) is chilled to 0 °C. Iodotrimethylsilane (5 mL, 37 mmol) is added via syringe. After complete reaction, it is diluted with diethyl ether and washed with 1 N HCl. Then it is concentrated aqueous with methanol titration to yield HCl salt of product. LCMS characterization ES+ 259.1 (m+1).

(2S,5R)-5-Allyl-1-((S)-2-methylamino-pent-4-enoyl)-pyrrolidine-2-carboxylic acid phenethyl-amide (11F)

AllylGlyOH (10.5 g, 26.4 mmol) is suspended in dichloromethane (200 mL) and EDCI (5.1 g, 26.4 mmol) and DMAP (3.2 g, 26.4 mmol) are added to obtain a clear solution. **11E** homoallylproline amide in dichloromethane (50 mL) is added and stirred overnight. The product is quenched with saturated bicarb and extracted with dichloromethane, followed by washing with brine, drying over anhydrous magnesium sulfate, filtering and concentrating. The crude is used in following deprotection. LCMS characterization ES+ 456.1 (m+1).

(2S,5R)-5-Allyl-1-((S)-2-amino-pent-4-enoyl)-pyrrolidine-2-carboxylic acid phenethyl-amide (11G)

Product **11F** is reconstituted in dichloromethane (40 mL) and added trifluoroacetic acid (10 mL). Stirring until reaction complete by HPLC. Toluene is added and concentrated to an amber oil. The product is dissolved in dichloromethane and washed with saturated bicarb followed by drying over anhydrous magnesium sulfate, filtering and concentrating to an amber solid. LCMS characterization ES+ 356.1 (m+1).

(2S,5R)-5-Allyl-1-[(S)-2-((S)-2-dimethylamino-propionylamino)-pent-4-enoyl]-pyrrolidine-2-carboxylic acid phenethyl-amide (11H)

Boc-N-MeAlaOH (5.36 g, 26.4 mmol) is suspended in dichloromethane (200 mL) and EDCI (5.4 g, 28 mmol) and DMAP (3.4 g, 28 mmol) are added to obtain a clear solution. **11G** in dichloromethane (50 mL) is added and stirred overnight followed by quenching with saturated bicarb and extracting with dichloromethane then washing with brine, drying over anhydrous magnesium sulfate, filtering and concentrating. LCMS characterization ES+ 541.2 (m+1).

(Z)-(3S,6S,10aR)-6-((S)-2-Dimethylamino-propionylamino)-5-oxo-1,2,3,5,6,7,10,10a-octahydro-pyrrolo[1,2-a]azocine-3-carboxylic acid phenethyl-amide (11I)

Product **11G** (894 mg) is dissolved in dichloromethane (50 mL) in a sealed tube under argon. Grubbs generation 2 catalyst (160 mg) is added and heated to 50 °C, venting every half hour. After 6 hours, the product is concentrated and filtered through SiO_2 with 10% methanol in ethyl acetate. Concentrating and isolating product by HPLC purification. LCMS characterization ES+ 513.2 (m+1).

(Z)-(3S,6S,10aR)-6-((S)-2-Methylamino-propionylamino)-5-oxo-1,2,3,5,6,7,10,10a-octahydro-pyrrolo[1,2-a]azocine-3-carboxylic acid phenethyl-amide (12)

Product **11I** is reconstituted in 20% trifluoroacetatic acid in dichloromethane (50 mL). Stirring until reaction complete by HPLC. Toluene is added and concentrated to an amber oil. The product is dissolved in dichloromethane and washed with saturated bicarb followed by drying over anhydrous magnesium sulfate, filtering and concentrating. HPLC purification to yield **12**. LCMS characterization ES+ 413.1 (m+1).

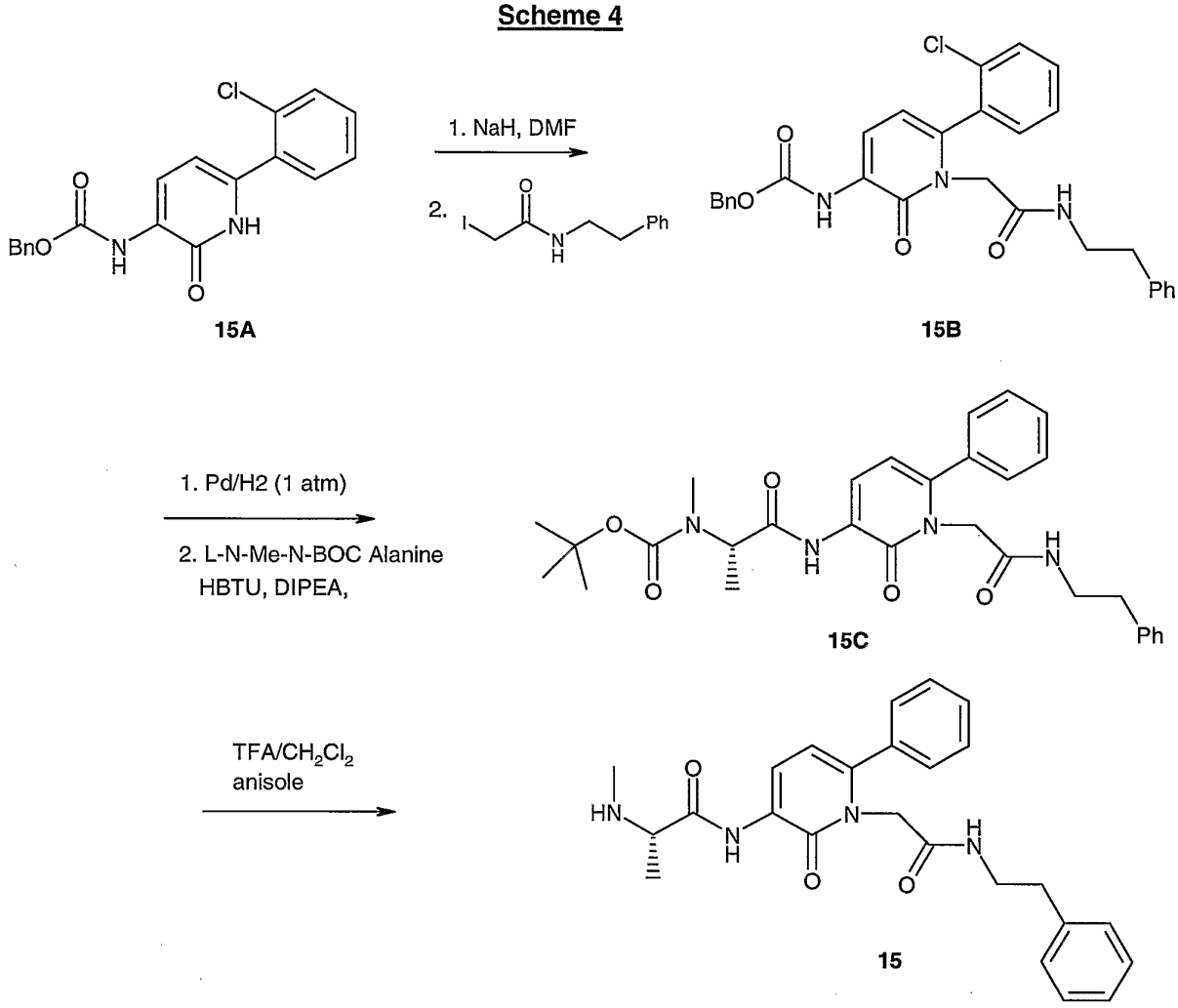
(Z)-(2S,5S)-5-Ethyl-1-[(S)-2-((S)-2-methylamino-propionylamino)-pentanoyl]-pyrrolidine-2-carboxylic acid phenethyl-amide (11)

Product **12** bicyclic olefin (5 mg) is dissolved in ethyl acetate (2 mL) under N_2 atmosphere and added 10% palladium on carbon (20 mg). It is purged with H_2 and stirred vigorously for 1 hour followed by filtering and concentrating to obtain **11**. LCMS characterization ES+ 415.1 (m+1).

Example 3 Synthesis of (S)-2-methylamino-N-[2-oxo-1-(phenethylcarbamoyl-methyl)-6-phenyl-1,2-dihydro-pyridin-3-yl]-propionamide (15)

The title compound **15** (formula 1) is prepared according to the procedure set forth in Scheme 4.

Scheme 4



[6-(2-Chloro-phenyl)-2-oxo-1-(phenethylcarbamoyl-methyl)-1,2-dihydro-pyridin-3-yl]-carbamic acid benzyl ester (15B)

To a suspension of NaH (60% in mineral oil, 287 mg, 7.17 mmol, 1.2 eq.) in anhydrous DMF (12 mL) is added [6-(2-chloro-phenyl)-2-oxo-1,2-dihydro-pyridin-3-yl]-carbamic acid benzyl ester (**15A**) (Bernstein, P.R. et. al., J. Med. Chem., vol. 37, p 3313-3326 (1994)) (2.121 g, 5.98 mmol). After being stirred for 30 minutes, the orange solution is cooled to 0 °C and 2-iodo-N-phenethyl-acetamide (1.902 g, 6.58 mmol, 1.1 eq.) is added. The mixture is stirred at room temperature for 3 hours and is quenched with 1 N HCl (8 mL), extracted with ethyl acetate (3 x). The organic layer is washed in sequence with 1 N HCl, saturated $Na_2S_2O_3$, water and brine; is dried over anhydrous Na_2SO_4 and concentrated. The residue is purified

via silica gel chromatography (2-10% ethyl acetate in dichloromethane) to provide compound **15B** as a yellow solid (605 mg, 20%):

^{1}H NMR (400 MHz, DMSO): δ 8.52 (bs, 1H), 7.96 (m, 1H), 7.93 (d, J = 8H, 1H), 7.63-7.07 (m, 14H), 6.22 (d, J = 8 Hz, 1H), 5.20 (bs, 2H), 4.89-3.75 (AB q, 2H), 3.20-3.11 (m, 2H), 2.57 (t, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, MSO): δ 165.7, 157.0, 153.2, 139.1, 138.8, 136.4, 133.1, 132.6, 132.1, 131.4, 129.3, 128.5, 128.4, 128.3, 127.9, 129.8, 127.7, 127.5, 126.0, 121.0, 107.1, 66.1, 47.7, 40.2, 34.8; MS (ESI) *m/e* 516 ($M+H^+$), 395.

Methyl-{(S)-1-[2-oxo-1-(phenethylcarbamoyl-methyl)-6-phenyl-1,2-dihydro-pyridin-3-ylcarbamoyl]-ethyl}-carbamic acid tert-butyl ester (15C)

To compound **15B** (595 mg, 1.15 mmol) above in anhydrous ethanol (24 mL) is added sodium methoxide (65 mg, 1.21 mmol) and palladium on carbon (10%, 236 mg, 40%). The mixture is hydrolyzed under hydrogen (1 atm) for 4 days. The mixture is filtered and washed with methanol. The filtrate is concentrated and the resulting residue is dissolved in anhydrous DMF (2 mL) followed by treatment at 0 °C with a solution prepared below: To (S)-N-methyl-N-BOC-alanine (240 mg, 1.18 mmol, 1.05 eq.) in anhydrous acetonitrile (2 mL) is added Hunig base (390 µL, 2.24 mmol, 2 eq.) and HBTU (447 mg, 1.18 mmol, 1.05 eq.) at 0 °C and kept at temperature for 30 minutes. The whole reaction mixture is stirred at room temperature for 36 hours and 50 °C for 7 hours; and quenched with water and 1 N HCl (2 mL). The mixture is extracted with ethyl acetate (3 x). The organic layer is washed with water and brine; dried over anhydrous Na_2SO_4. Upon concentration the residue is purified through silica gel chromatography (20-30% ethyl acetate in hexane) to provide compound **15C** as a white solid (86 mg, 15%):

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (bs, 1H), 8.34 (d, J = 8 Hz, 1H), 7.35-7.04 (m, 10H), 6.19 (bs, 1H), 6.13 (d, J = 8H), 4.35 (AB q, 2H), 4.06 (q, J = 4 Hz, 1H), 3.42 (m, 2H), 2.79 (bs, 3H), 2.71 (t, J = 4 Hz, 2H), 1.36 (d, J = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 167.0, 158.1, 155.5, 142.8, 138.6, 134.5, 129.4, 129.3, 128.7, 128.6, 128.5, 127.8, 126.5, 122.3, 108.6, 80.9, 40.8, 35.5, 29.3, 28.3, 14.1, 13.7; MS (ESI) *m/e* 522 ($M+H^+$).

(S)-2-Methylamino-N-[2-oxo-1-(phenethylcarbamoyl-methyl)-6-phenyl-1,2-dihydro-pyridin-3-yl]-propionamide (15)

Compound **15C** (74 mg, 0.14 mmol) from above is treated with anisole (45 µL, 0.42 mmol) and TFA (1 mL) in anhydrous dichloromethane (1 mL) for 4 hours. The mixture is concentrated and the residue is treated with dichloromethane (1 mL). The solution is added

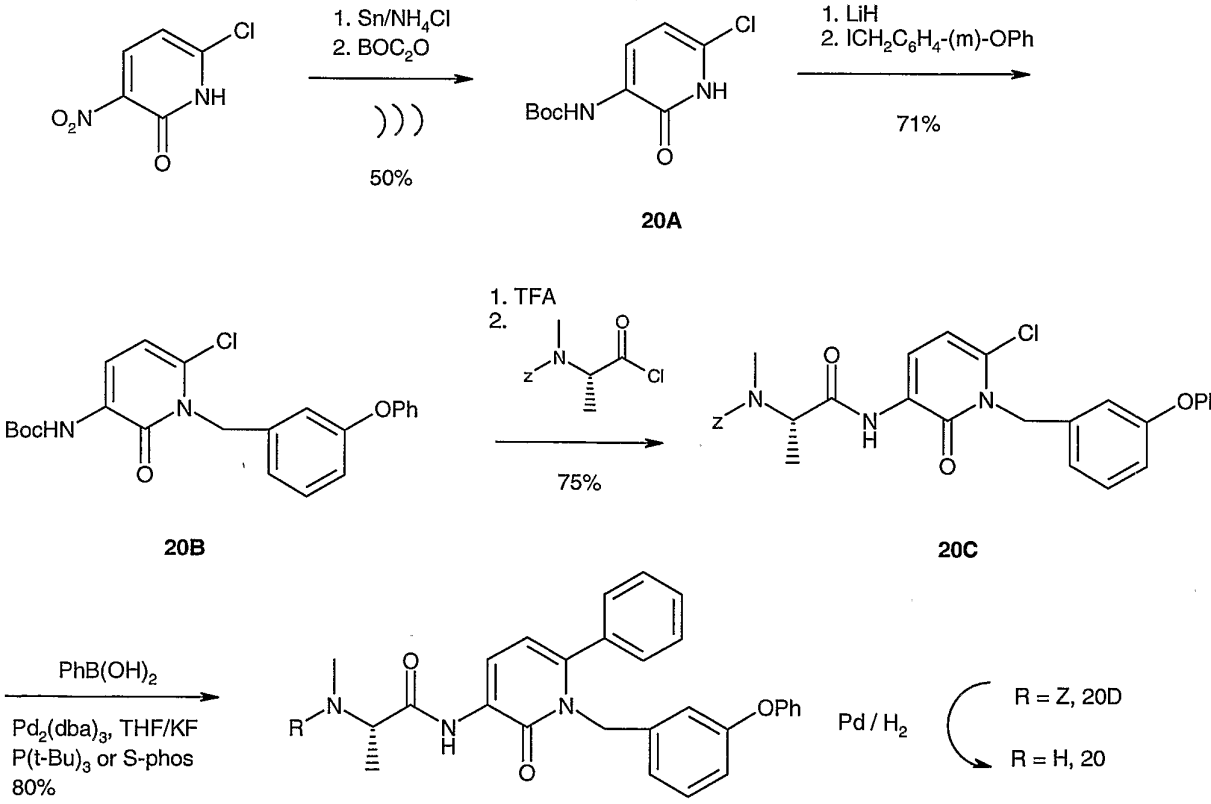
dropwise to a rapidly stirring mixture of hexane and anhydrous ether (10.5 mL). The resulting slurry is filtered, leaving a white solid that is washed with the same solvent mixture twice and dried in vacuo to afford compound **1** as a TFA salt (45 mg, 59%):

^{1}H NMR (400 MHz, DMSO): δ 10.08 (s, 1H), 8.83 (bs, 2H), 8.22 (d, J = 8 Hz, 1H), 8.05 (t, J = 4 Hz, 1H), 7.44-7.08 (m, 10H), 6.18 (d, J = 8 Hz, 1H), 4.32 (s, 2H), 4.18 (q, J = 4 Hz), 3.19 (m, 2H), 2.59 (t, J = 8 Hz), 2.43 (bs, 3H), 1.39 (d, J = 3 Hz, 3H); ^{13}C NMR (100 MHz, DMSO): δ 168.5, 166.4, 157.6, 157.1, 144.1, 139.2, 134.7, 129.3, 128.7, 128.6, 128.5, 128.3, 126.6, 126.1, 124.1, 106.6, 56.7, 49.0, 35.0, 30.9, 16.0; *MS (ESI) m/e* 433 (M+H$^+$), 312.

Example 4 Synthesis of (S)-N-[6-phenyl-2-oxo-1-(3-phenoxy-benzyl)-1,2-dihydro-pyridin-3-yl]-2-methylamino-propionamide (20)

The title compound **20** (formula 1) is prepared according to the procedure set forth in Scheme 5:

Scheme 5



(6-Chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-carbamic acid tert-butyl ester (20A)

A suspension of tin powder (2 g, 17.20 mmol, 2.5 eq.), ammonium chloride (2.576 g, 48.16 mmol, 7 eq.) and 6-chloro-3-nitro-1H-pyridien-2-one (1.201 g, 6.88 mmol, Moody, C.J. et al., J. Chem. Soc. Perkin Trans I, p 955 (2001)) in anhydrous methanol (14 mL) is sonicated for 3 hours. The solvent is removed from the mixture by rotary evaporation. The residue is treated with anhydrous THF (14 mL) and Boc anhydride (3.00 g, 13.76 mmol, 2 eq.) and the mixture is heated at reflux for 18 hours. More Boc anhydride (0.90 g, 0.6 mmol) is added to the mixture and reflux continued for 14 hours. The mixture is filtered through a silica gel pad with 2% methanol in methylene chloride washing. The filtrate is concentrated and the residue is purified by silica gel chromatography (0-2% methanol in methylene chloride) to afford the title compound **20A** (1.12 g, 58.9%):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (bd, J = 8 Hz,1H), 7.33 (bs, 1H), 71.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 152.6, 127.8, 126.5, 122.6, 107.6, 81.2, 28.3; MS (ESI) *m/e* 245 ($M+H^+$), 191, 189 (U3910-65).

6-Chloro-2-oxo-1-(3-phenoxy-benzyl)-1,2-dihydro-pyridin-3-yl]-carbamic acid tert-butyl ester (20B)

To lithium hydride (53 mg, 6,67 mmol) in anhydrous DMF/DME (7.6/2.6 mL) is added at 0 °C pyridone **20A** (1.255 g, 5.13 mmol). The mixture is stirred at room temperature for 30 minutes, then 3-phenoxy-benzyl iodide (1.43 mL, 7.19 mmol) is added and the mixture is heated at 75 °C for 3 hours. The reaction mixture is quenched with icy water and extracted with ethyl acetate (3 x). The organic phase is washed with brine (5 x), dried over anhydrous sodium sulfate. Upon filtration and concentration the residue showed the presence of ca. 80/20 of the N-/O-alkylation products by ^{1}H NMR (the two structures were distinguished by HMBC). The crude product is purified by silica gel chromatography (2.5-5.0% ethyl acetate in hexane) to afford the desired pyridone **20B** (1.544 g, 70.5%):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (bs, d, J = 8 Hz,1H), 7.51 (bs, 1H), 71.28-6.81 (m, 9H), 6.28 (d, J = 8 Hz, 1H); ^{13}C NMR (100 MHz,$CDCl_3$): δ 158.1, 157.6, 156.9, 152.7, 137.6, 130.0, 129.8, 128.6, 127.7, 123.4, 121.9, 119.2, 117.9, 117.8, 107.3, 81.0, 49.5, 28.2; MS (ESI) m/e 427 (M+H+), 371 (U3910-76).

{(S)-1-[6-Chloro-2-oxo-1-(3-phenoxy-benzyl)-1,2-dihydro-pyridin-3-ylcarbamoyl]-ethyl}-methyl-carbamic acid benzyl ester (20C)

To compound **20B** (410 mg, 0.836 mmol) in anhydrous methylene chloride (0.65 mL) is added anisole (0.31 mL) and TFA (2.0 mL). The mixture is stirred for 2 hours and is added dropwise to a rapidly stirring mixture of methylene chloride and anhydrous ether (15/1 mL). The top solution is decanted and the bottom oil is dried *in vacuo*. The greenish amine residue is dissolved in anhydrous methylene chloride (2.5 mL) with 2,4,6-trimethylpyridine (0.39 mL, 2.93 mmol).

In another flask is placed L-N-methyl Z-analine (536 mg, 2.26 mmol) and methylene chloride (2.5 mL). The mixture is treated at 0 °C with 1-chlroine-N,N,2-trimethylpropenylamine (0.30 mL, 2.26 mmol). The reaction mixture is stirred at 0 °C for 20 minutes and at the same temperature, is treated with the above mentioned amine solution. After being stirred at 0 °C for 2 hours and room temperature for 1 hour, the reaction mixture is concentrated. The residue is quenched with water and extracted with ethyl acetate (3 x). The organic phase is washed with saturated citric acid, saturated sodium bicarbonate and brine (3 x), dried over anhydrous sodium sulfate. Upon filtration, concentration and purification by silica gel chromatography (15-20% ethyl acetate in hexane) the desired compound **20C** (363 mg, 75.0%) is obtained:

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (bs, 1H), 8.30 (bs, 1H), 7.35-6.86 (m, 14H), 6.36 (d, J = 8 Hz, 1H), 5.46 (AB, 2H), 5.29 (br, 2H), 5.19-4.98 (b, 1H), 2.92 (bs, 3H), 1.43 (d, J = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 158.2, 157.6, 156.8, 137.4, 136.3, 130.1, 129.8, 129.6, 128.5, 128.1, 127.7, 123.5, 122.0, 121.8, 119.1, 117.8, 107.2, 67.9, 55.8, 49.6, 30.0, 14.4; MS (ESI) m/e 546 ($M+H^+$) (U3910-80, 83 and 100).

{(S)-1-[6-Phenyl-2-oxo-1-(3-phenoxy-benzyl)-1,2-dihydro-pyridin-3-ylcarbamoyl]-ethyl}-methyl-carbamic acid benzyl ester (20D)

To a mixture of compound **20C** (37 mg, 0.068 mmol), phenyl boronic acid (12 mg, 0.10 mmol) tri-tert-butylphosphonium tetra fluoroborate (16 mg, 0.054 mmol), tris(dibenzylideneacetone) dipalladium (12 mg, 0.027 mmol) and potassium floride (61 mg, 1.0 mmol) is added under nitrogen atmosphere anhydrous THF (1.0 mL). The mixture is heated at reflux for 20 hours and is concentrated. The residue is purified by silica gel preparative TLC (40% ethyl acetate in hexane) to provide the title compound **20D** (32 mg, 80%):

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.90 (bs, 1 H), 8.32 (bs, 1H), 7.33-7.00 (m, 14H), 6.86 (m, 2H), 6.75 (dd, J = 8, 8 Hz, 1H), 6.58 (m, 1H), 6.43 (bs, 1H), 6.10 (d, J = 8 Hz, 1H), 5.18-4.75 (m, 5H), 2.88 (bs, 3H), 1.39 (d, J = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 158.0, 157.5, 156.8, 142.7, 138.7, 134.9, 129.9, 129.7, 129.2, 129.1, 128.5, 128.4, 128.1, 123.4, 122.0, 121.4, 119.1, 117.5, 117.0, 108.5, 64.8, 55.8, 49.2, 30.1, 13.8; MS (ESI) *m/e* 588 ($M+H^+$) (U3910-108).

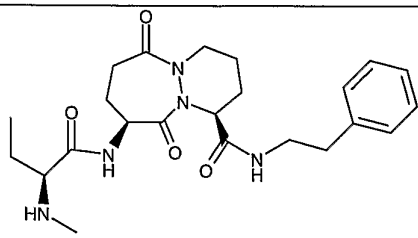
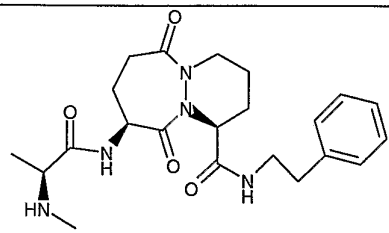
(S)-N-[6-Phenyl-2-oxo-1-(3-phenoxy-benzyl)-1,2-dihydro-pyridin-3-yl]-2-methylamino-propionamide (20)

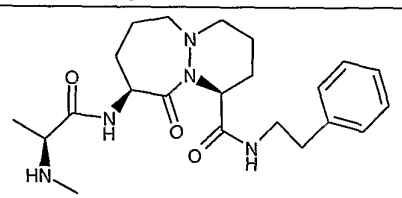
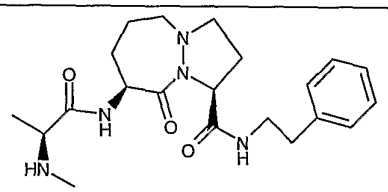
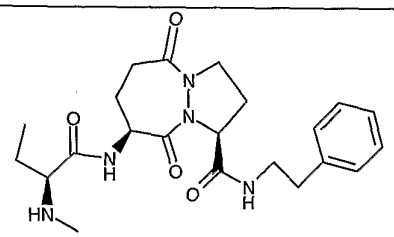
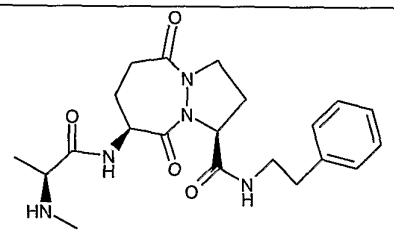
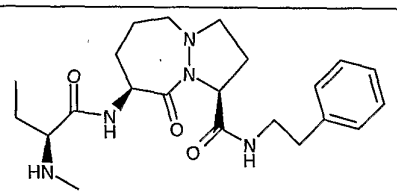
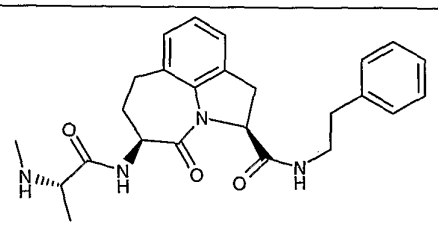
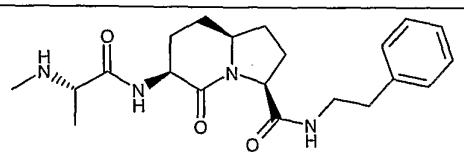
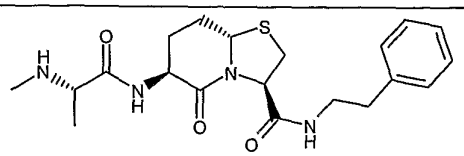
Compound **20D** (55 mg, 0.094 mmol) in ethanol (2 mL) is hydrogenated under 10% palladium on carbon (10 mg) and hydrogen (balloon pressure). The reaction is monitored by LCMS. Upon completion the mixture is filtered and the filtrate is concentrated and purified by HPLC to afford the title compound (5 mg, 12%):

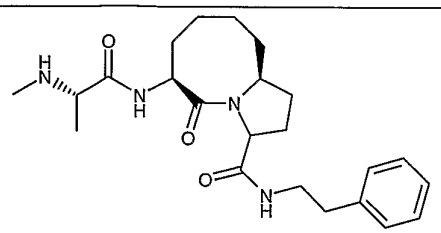
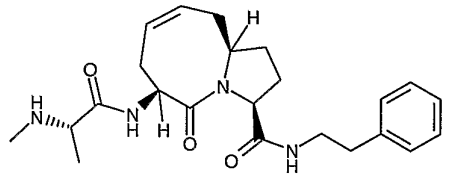
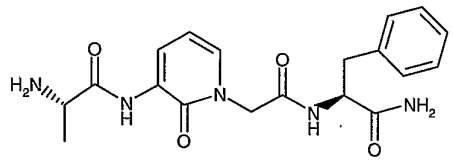
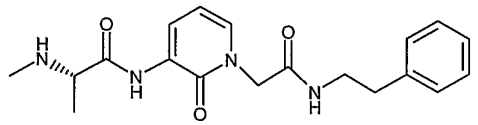
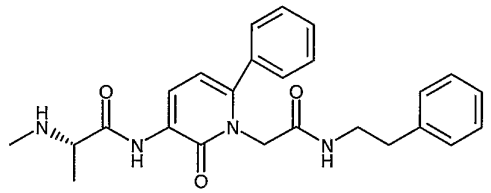
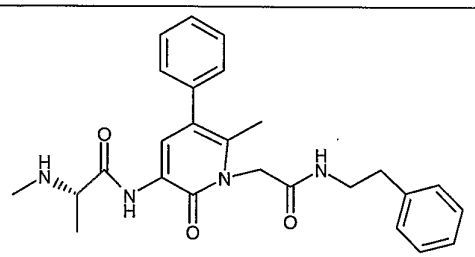
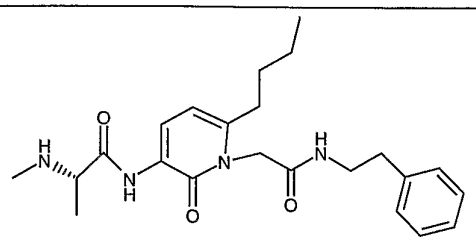
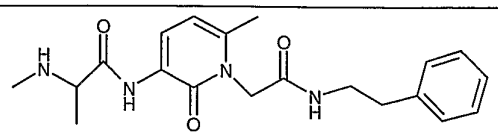
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 (bs, 1H), 8.33 (d, J = 8 Hz, 1H), 7.36-7.02 (m, 9H), 6.85 (d, J = 8 Hz, 2H), 6.75 (dd, J = 8, 8 Hz, 1H), 6.56 (d, J = 8 Hz, 1H), 6.42 (bs, 1 H), 6.17 (d, J = 6, 1H), 5.12 (bs, 2H), 4.06 (bs, 1H), 2.70 (bs, 3H), 1.62 (d, J = 4 Hz, 3H); MS (ESI) *m/e* 454 ($M+H^+$), (U3910-116).

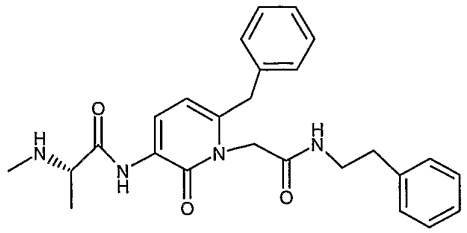
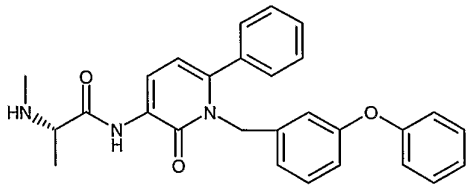
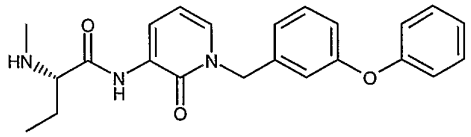
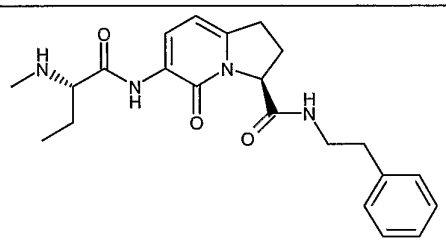
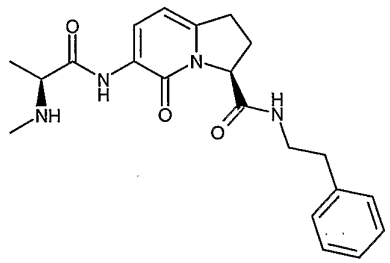
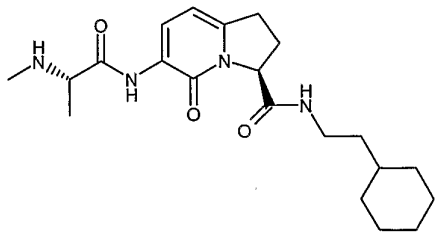
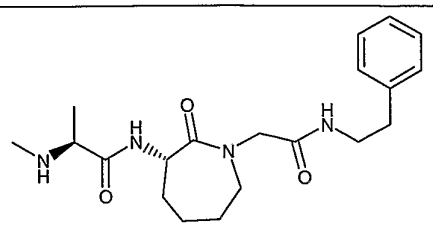
Examples 1-30

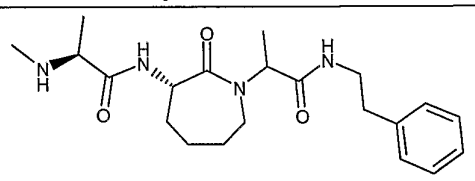
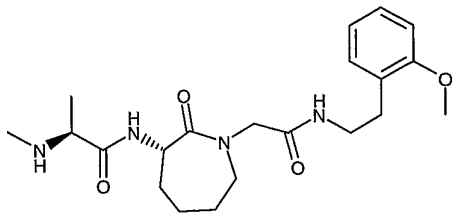
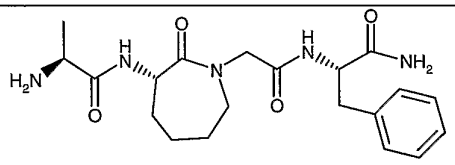
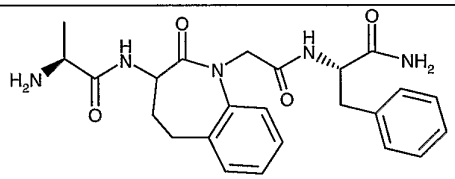
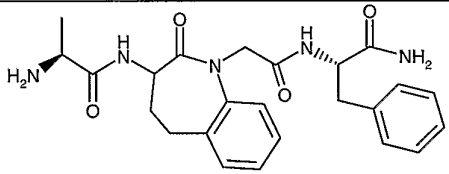
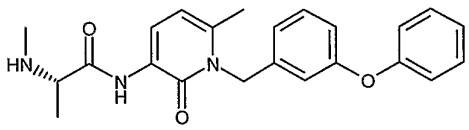
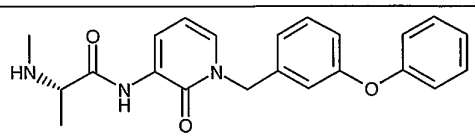
The following compounds are prepared by methods analogs to those described herein utilizing analogous starting materials:

Compound Structure	Example Number
	Example 1 MS ESI 444.55 $(M+H)^+$
	Example 2 MS ESI 430.52 $(M+H)^+$

Compound Structure	Example Number
	Example 3 MS ESI 416.54 $(M+H)^+$
	Example 4 MS ESI 402.51 $(M+H)^+$
	Example 5 MS ESI 430. 2 $(M+H)^+$
	Example 6 MS ESI 415.50 $(M+H)^+$
	Example 7 MS ESI 416.54 $(M+H)^+$
	Example 8 MS ESI 435.54 $(M+H)^+$
	Example 9 MS ESI 387.50 $(M+H)^+$
	Example 10 MS ESI 405.54 $(M+H)^+$

Compound Structure	Example Number
	Example 11 MS ESI 415.55 $(M+H)^+$
	Example 12 MS ESI 413.54 $(M+H)^+$
	Example 13 MS ESI 386.43 $(M+H)^+$
	Example 14 MS ESI 357.43 $(M+H)^+$
	Example 15 MS ESI 433.53 $(M+H)^+$
	Example 16 MS ESI 447.55 $(M+H)^+$
	Example 17 MS ESI 413.54 $(M+H)^+$
	Example 18 MS ESI 371.46 $(M+H)^+$

Compound Structure	Example Number
	Example 19 MS ESI 447.55 $(M+H)^+$
	Example 20 MS ESI 454.55 $(M+H)^+$
	Example 21 MS ESI 392.47 $(M+H)^+$
	Example 22 MS ESI 397.49 $(M+H)^+$
	Example 23 MS ESI 383.47 $(M+H)^+$
	Example 24 MS ESI 389.51 $(M+H)^+$
	Example 25 MS ESI 375.49 $(M+H)^+$

Compound Structure	Example Number
	Example 26 MS ESI 389.2 $(M+H)^+$
	Example 27 MS ESI 405.51 $(M+H)^+$
	Example 28 MS ESI 404.49 $(M+H)^+$
	Example 29 MS ESI 452.53 $(M+H)^+$
	Example 30 MS ESI 452.53 $(M+H)^+$
	Example 31 MS ESI 392.47 $(M+H)^+$
	Example 32 MS ESI 378.17 $(M+H)^+$

In order to measure the ability of the inventive compounds to bind the BIR3 peptide binding pocket, a solution phase assay on the FMAT or ELISA technology platform is utilized.

Fmat

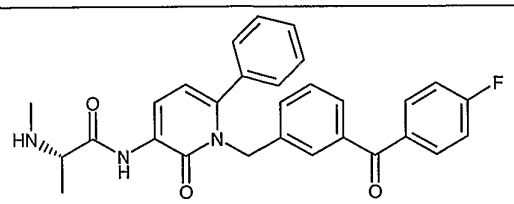
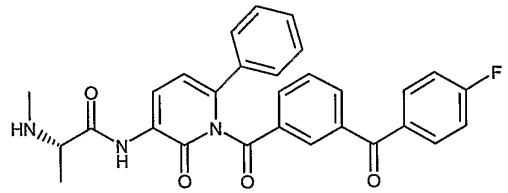
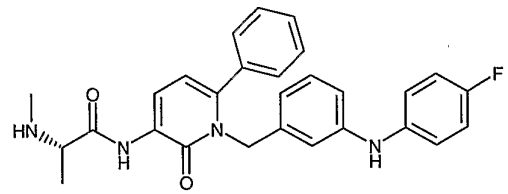
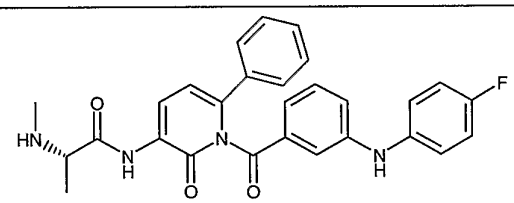
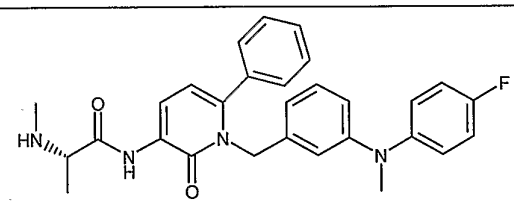
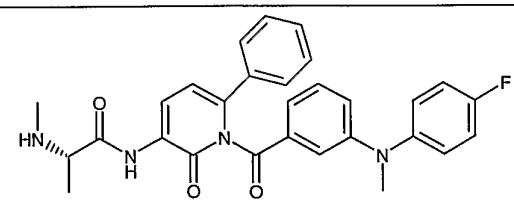
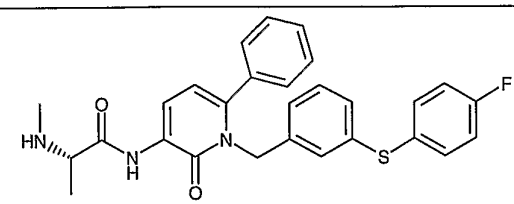
Biotinylated Smac 7-mer peptide (AVPIAQK, lysine ε-amino group is biotinylated) is immobilized on streptavidin coated beads. GST-BIR3 fusion protein is precipitated with FMAT beads and is detected using fluorescent tagged anti-GST antibodies. Importantly, non-biotinylated Smac peptide is highly effective at competing GST-BIR3 off the FMAT beads (Figure 2). The IC_{50} for non-biotinylated Smac is 400 nM. The IC_{50} values of compounds listed in Table 1 in the described FMAT assay ranged from 0.025-10 μM.

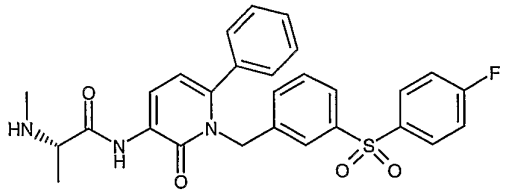
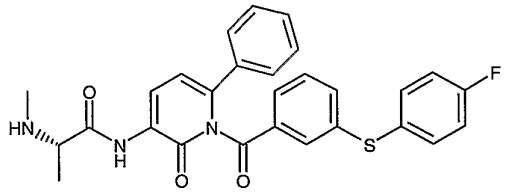
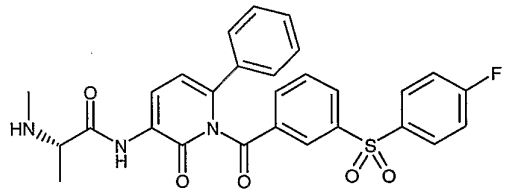
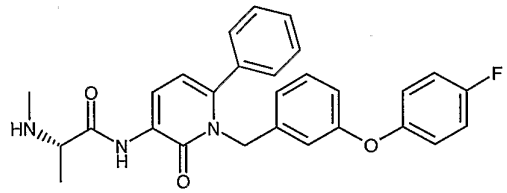
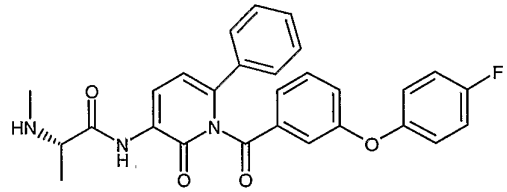
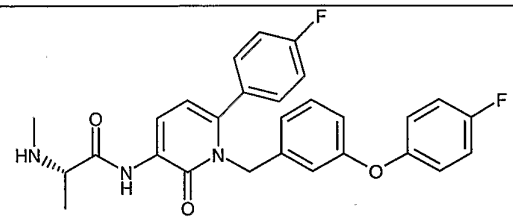
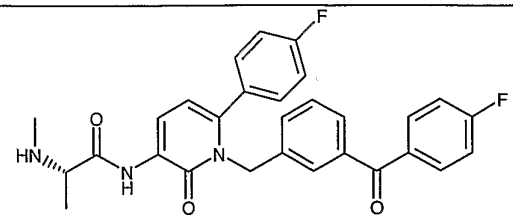
Elisa

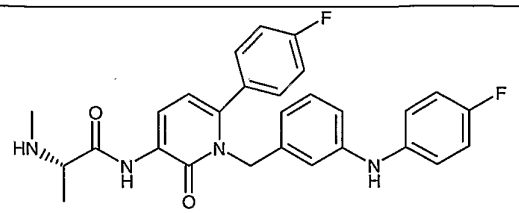
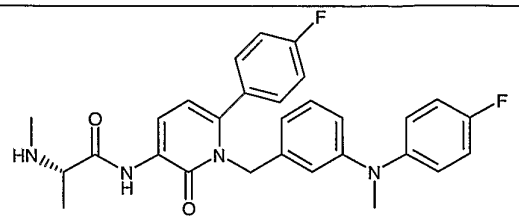
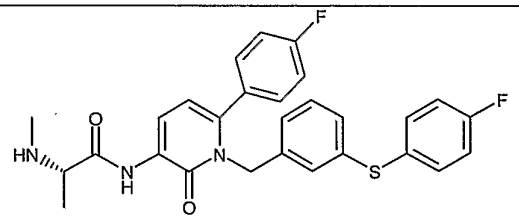
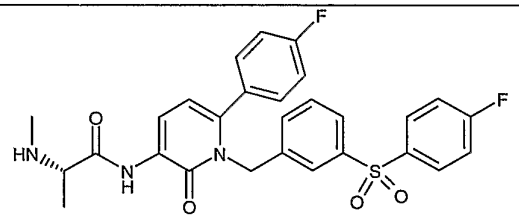
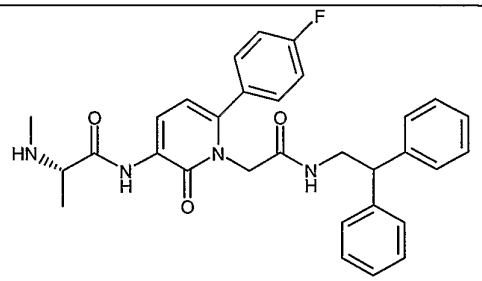
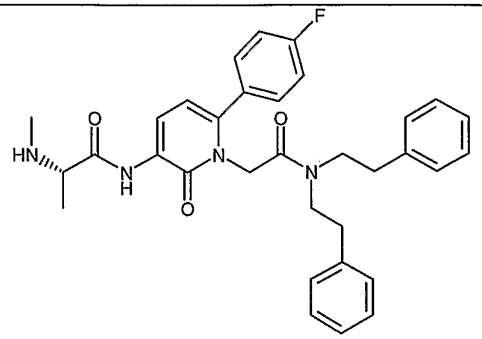
Compounds are incubated with GST-BIR3 fusion protein and biotinylated SMAC peptide (AVPFAQK) in stretavidin-coated 96-well plates. For XIAP BIR3 Smac Elisa, a GST-BIR3 fusion containing amino acids 248-358 from XIAP was used. For CIAP1 BIR3 Smac Elisa, a GST-BIR3 fusion containing amino acids 259-364 from CIAP1 was used. Following a 30-minute incubation, wells are extensively washed. The remaining GST-BIR3 fusion protein is monitored by ELISA assay involving first, incubation with goat anti-GST antibodies followed by washing and incubation with alkaline phosphatase conjugated anti-goat antibodies. Signal is amplified using Attophos (Promega) and read with Cytoflour Ex 450 nm/40 and Em 580 nm. IC_{50}s correspond to concentration of compound which displaces half of GST-BIR3 signal. The IC_{50} for non-biotinylated Smac is 400 nM. The IC_{50} values of compounds listed in Table 1 in the described ELISA assays ranged from 0.005-10 μM.

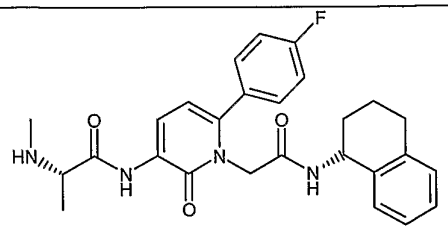
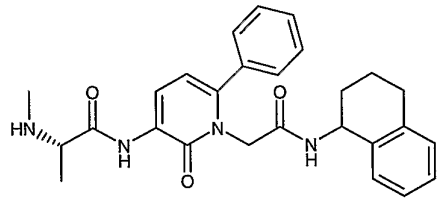
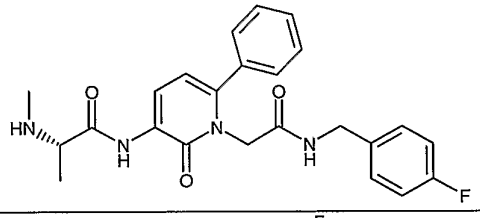
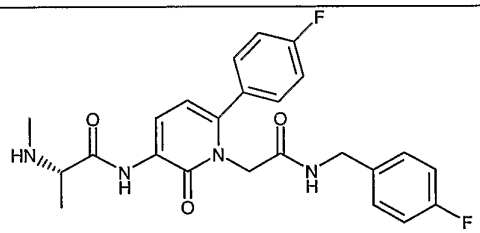
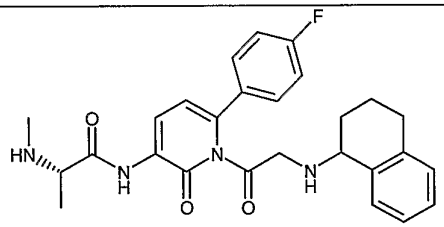
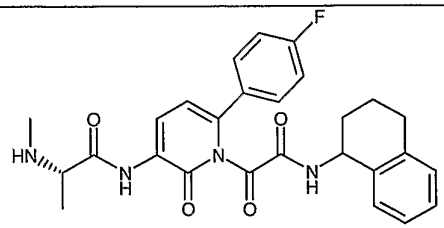
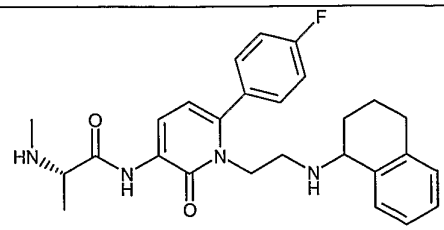
Cell Proliferation Assay

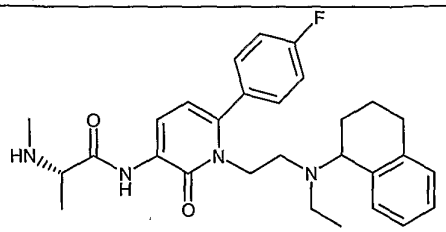
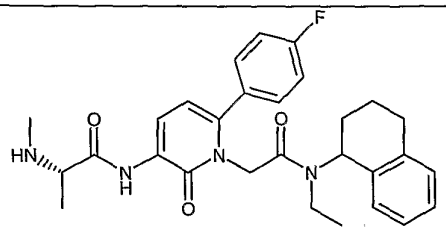
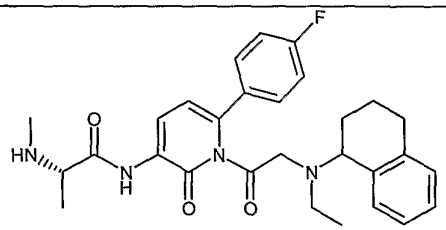
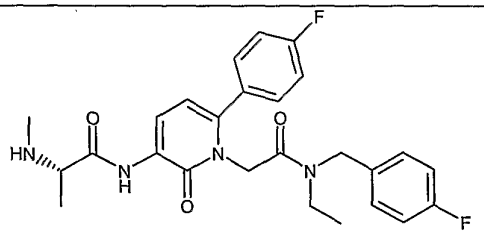
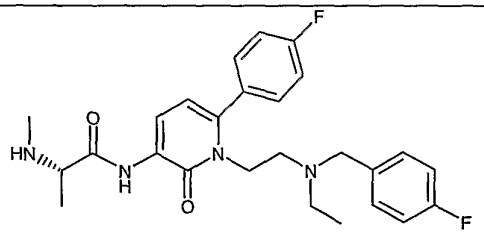
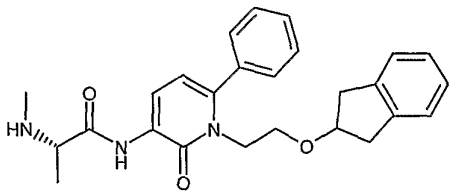
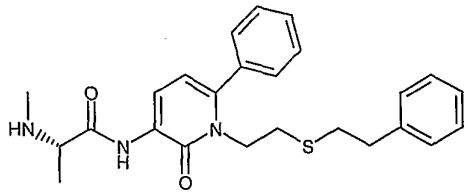
The ability of compounds to inhibit tumor cell growth *in vitro* was monitored using the CellTiter 96® AQ_{ueous} Non-Radioactive Cell Proliferation Assay (Promega). This assay is composed of solutions of a novel tetrazolium compound [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt; MTS] and an electron coupling reagent (phenazine methosulfate) PMS. MTS is bioreduced by cells into a formazan product, the absorbance of which is measured at 490 nm. The conversion of MTS into the aqueous soluble formazan product is accomplished by dehydrogenase enzymes found in metabolically active cells. The quantity of formazan product as measured by the amount of 490 nm absorbance is directly proportional to the number of living cells in culture. The IC_{50} values of compounds listed in Table 1 in the described cell assays ranged from 0.005-50 μM.

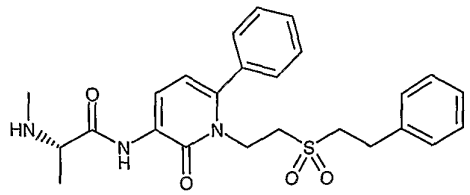
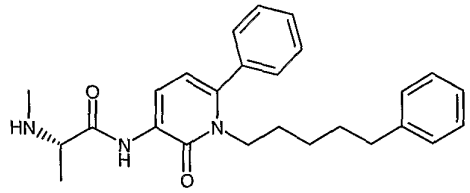
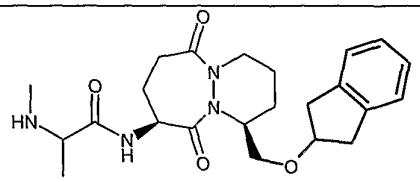
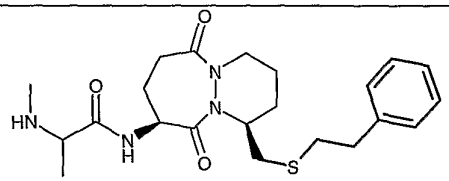
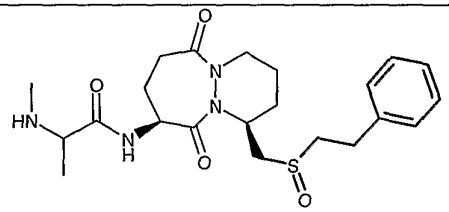
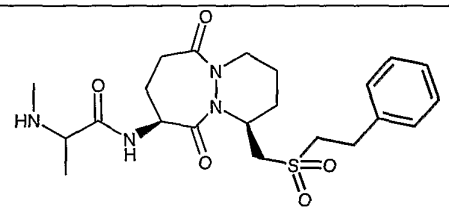
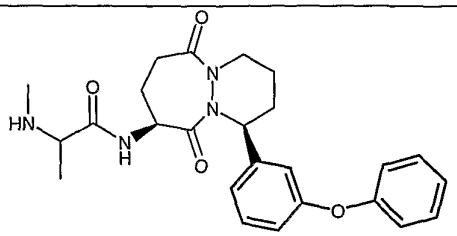
Compound Structure	Example Number
	Example 33 MS ESI 484.2 $(M+H)^+$
	Example 34 MS ESI 498.2 $(M+H)^+$
	Example 35 MS ESI 471.2 $(M+H)^+$
	Example 36 MS ESI 485.2 $(M+H)^+$
	Example 37 MS ESI 485.2 $(M+H)^+$
	Example 38 MS ESI 499.2 $(M+H)^+$
	Example 39 MS ESI 488.2 $(M+H)^+$

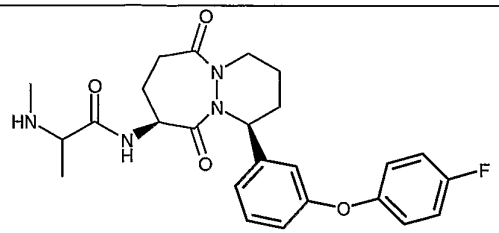
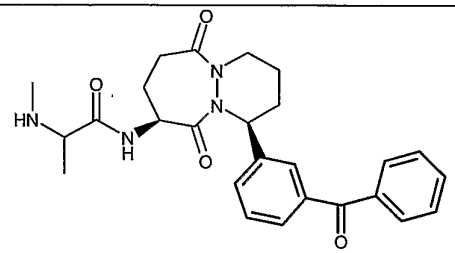
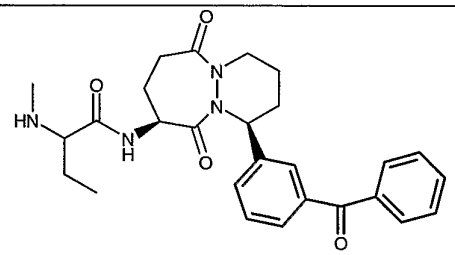
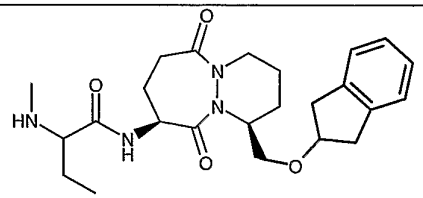
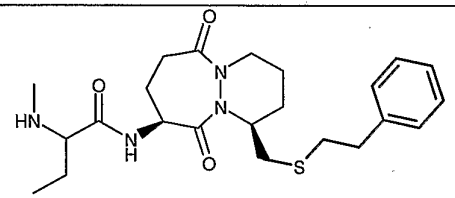
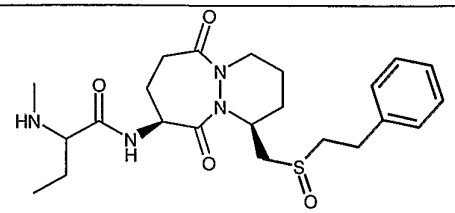
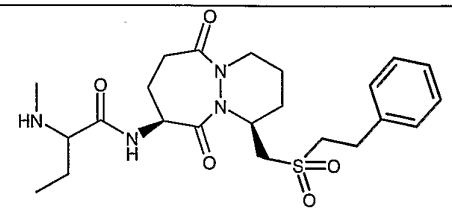
Compound Structure	Example Number
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	Example 41 MS ESI 502.2 $(M+H)^+$
	Example 42 MS ESI 534.1 $(M+H)^+$
	Example 43 MS ESI 472.2 $(M+H)^+$
	Example 44 MS ESI 486.2 $(M+H)^+$
	Example 45 MS ESI 490.2 $(M+H)^+$
	Example 46 MS ESI 502.8 $(M+H)^+$

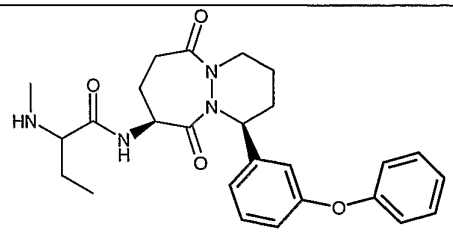
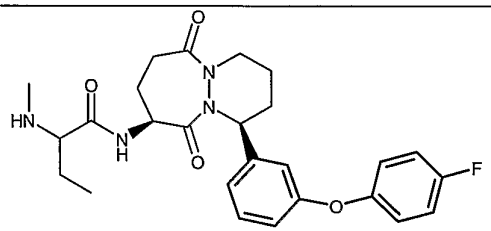
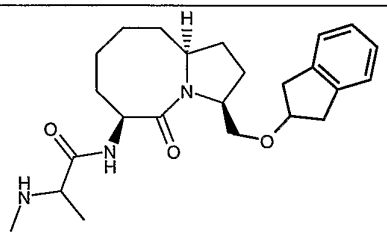
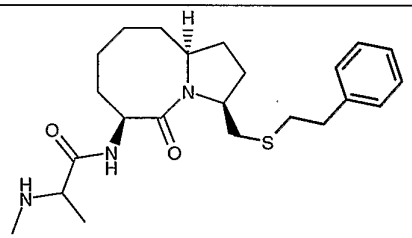
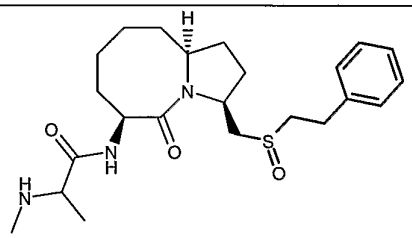
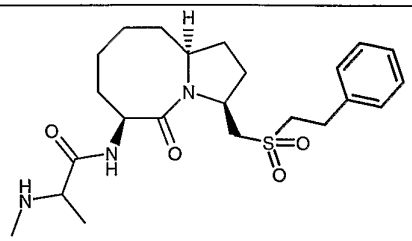
Compound Structure	Example Number
	Example 47 MS ESI 489.2 $(M+H)^+$
	Example 48 MS ESI 503.2 $(M+H)^+$
	Example 49 MS ESI 506. 2 $(M+H)^+$
	Example 50 MS ESI 538.2 $(M+H)^+$
	Example 51 MS ESI 527.2$(M+H)^+$
	Example 52 MS ESI 555.3 $(M+H)^+$

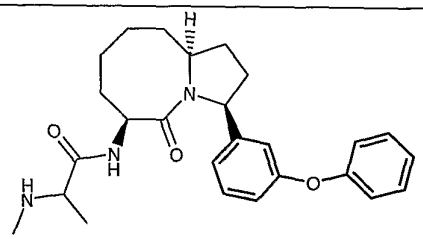
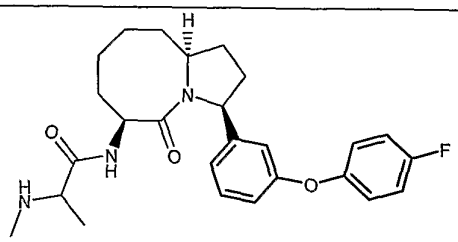
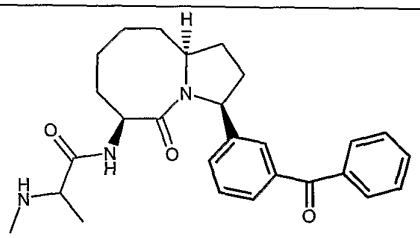
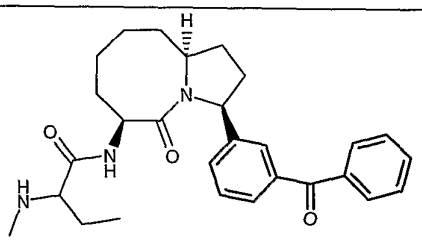
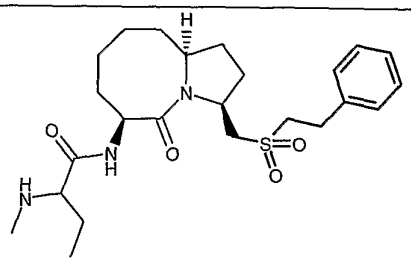
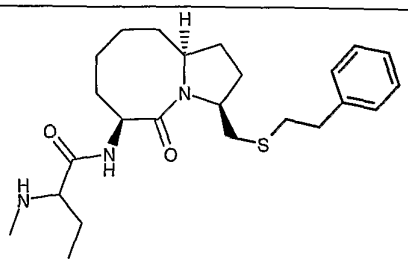
Compound Structure	Example Number
	Example 53 MS ESI 477.2 $(M+H)^+$
	Example 54 MS ESI 458.2 $(M+H)^+$
	Example 55 MS ESI 437.2 $(M+H)^+$
	Example 56 MS ESI 455.2 $(M+H)^+$
	Example 57 MS ESI 477.2 $(M+H)^+$
	Example 58 MS ESI 491.2 $(M+H)^+$
	Example 59 MS ESI 463.2 $(M+H)^+$

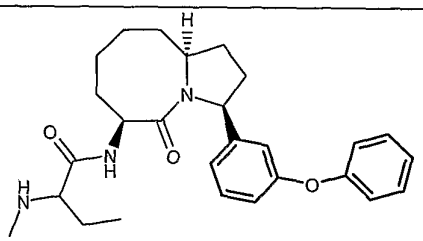
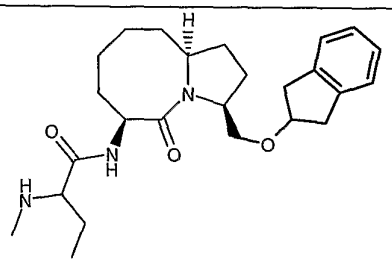
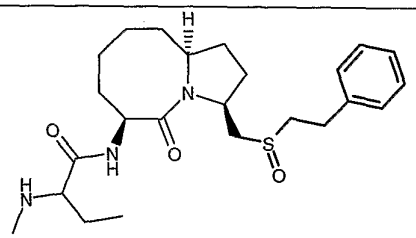
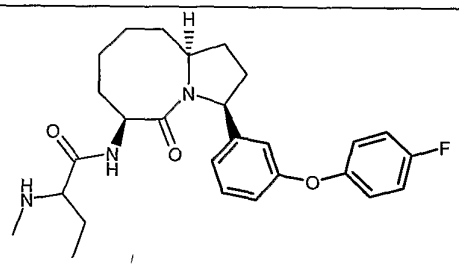
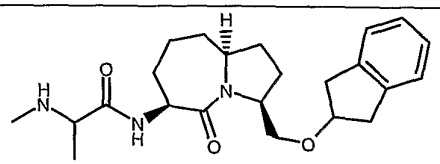
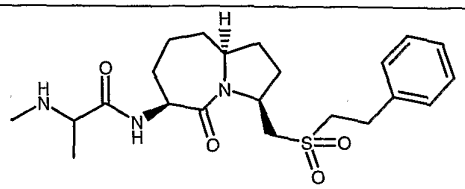
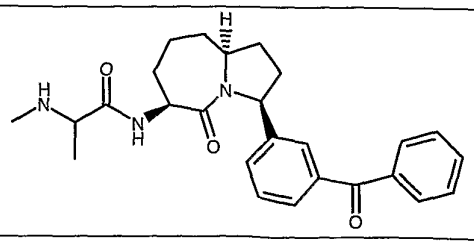
Compound Structure	Example Number
	Example 60 MS ESI 491.3 $(M+H)^+$
	Example 61 MS ESI 505.3 $(M+H)^+$
	Example 62 MS ESI 505.3 $(M+H)^+$
	Example 63 MS ESI 483.2 $(M+H)^+$
	Example 64 MS ESI 468.2 $(M+H)^+$
	Example 65 MS ESI 432.2 $(M+H)^+$
	Example 66 MS ESI 436.2 $(M+H)^+$

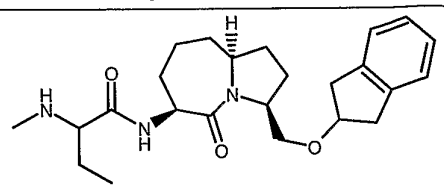
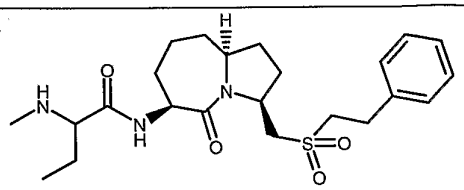
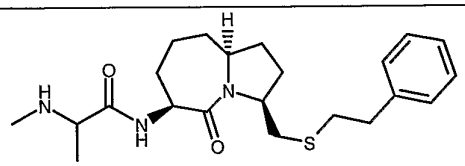
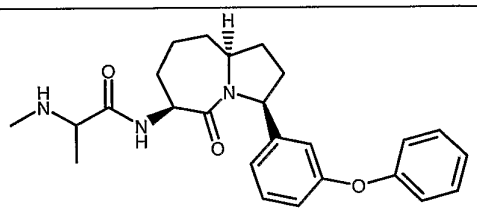
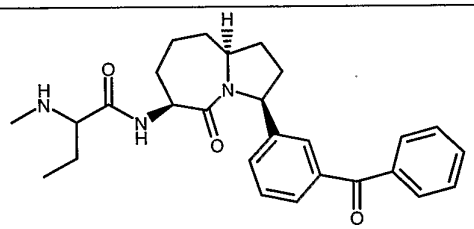
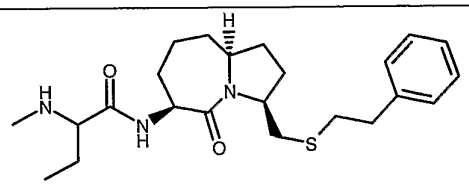
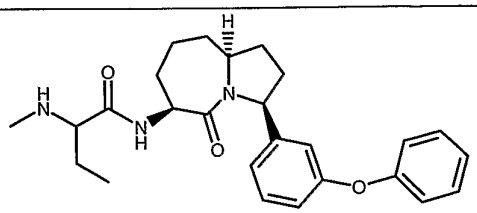
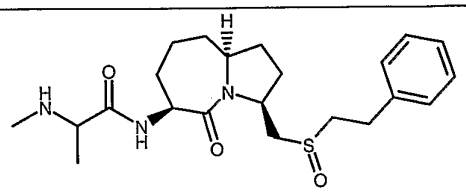
Compound Structure	Example Number
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	Example 68 MS ESI 418.2 $(M+H)^+$
	Example 69 MS 429.2 $(M+H)^+$
	Example 70 MS 433.2 $(M+H)^+$
	Example 71 MS 449.2 $(M+H)^+$
	Example 72 MS 465.2 $(M+H)^+$
	Example 73 MS 451.2 $(M+H)^+$

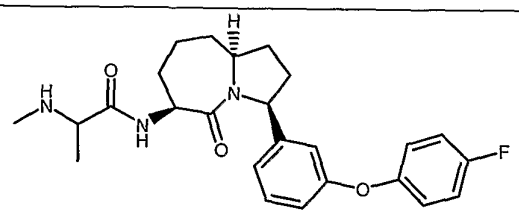
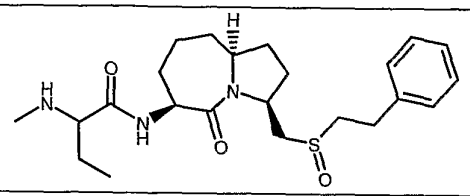
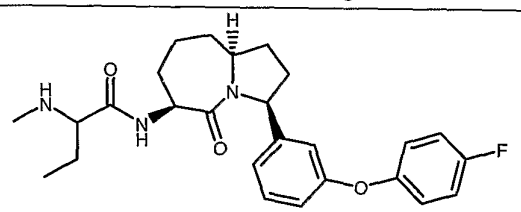
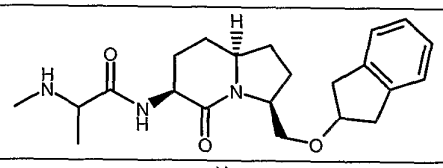
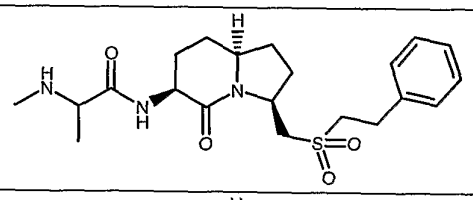
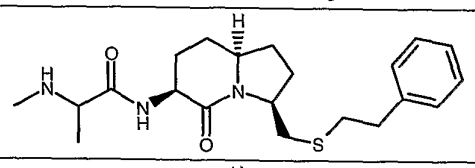
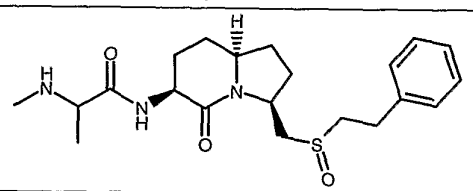
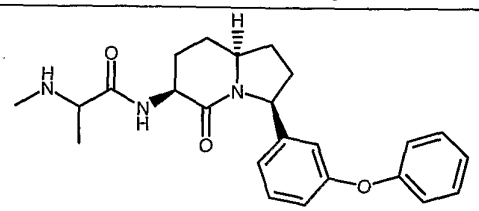
Compound Structure	Example Number
	Example 74 MS 469.2 $(M+H)^+$
	Example 75 MS 463.2 $(M+H)^+$
	Example 76 MS 476.2 $(M+H)^+$
	Example 77 MS 443.3 $(M+H)^+$
	Example 78 MS 447.2 $(M+H)^+$
	Example 79 MS 463.2 $(M+H)^+$
	Example 80 MS 479.2 $(M+H)^+$

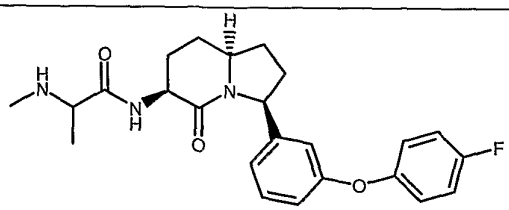
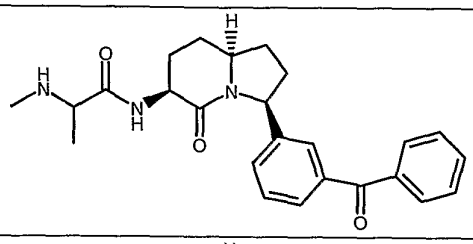
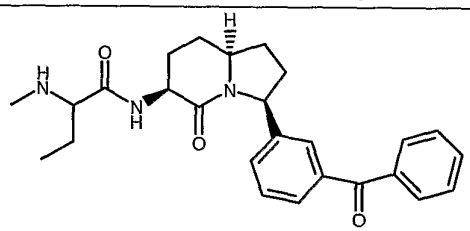
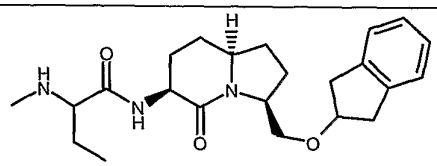
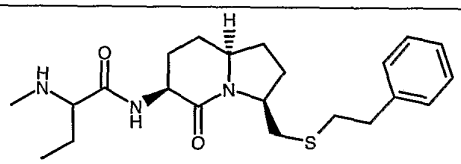
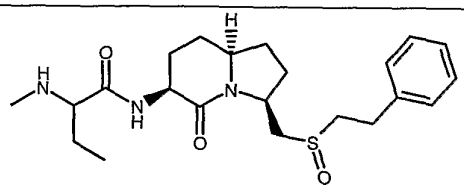
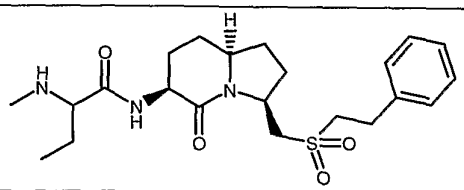
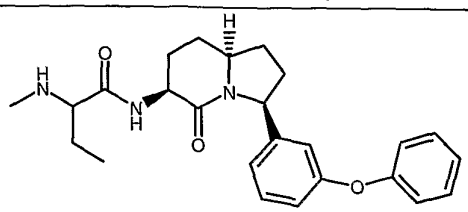
Compound Structure	Example Number
	Example 81 MS 465.2 $(M+H)^+$
	Example 82 MS 483.2 $(M+H)^+$
	Example 83 MS 414.3 $(M+H)^+$
	Example 84 MS 418.3 $(M+H)^+$
	Example 85 MS 434.2 $(M+H)^+$
	Example 86 MS 450.2 $(M+H)^+$

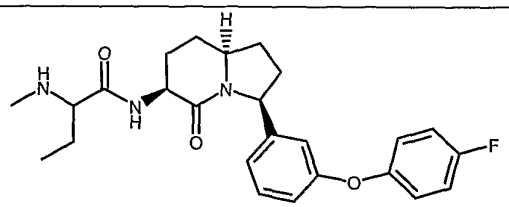
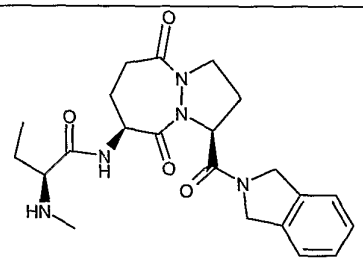
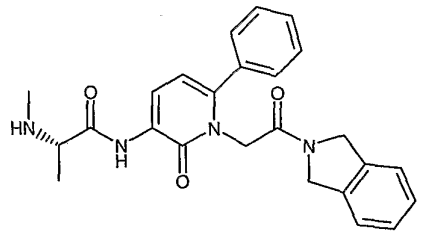
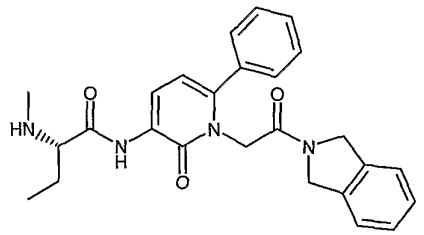
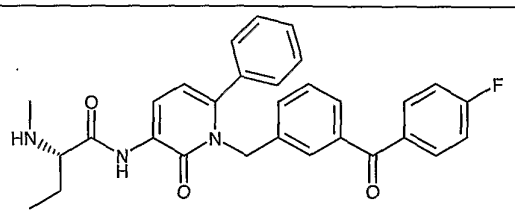
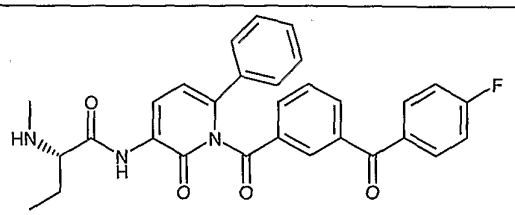
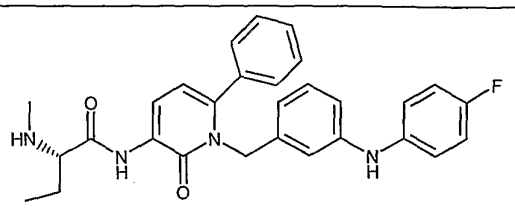
Compound Structure	Example Number
	Example 87 MS 436.3 $(M+H)^+$
	Example 88 MS 454.2 $(M+H)^+$
	Example 89 MS 448.3 $(M+H)^+$
	Example 90 MS 462.3 $(M+H)^+$
	Example 91 MS 464.3 $(M+H)^+$
	Example 92 MS 432.3 $(M+H)^+$

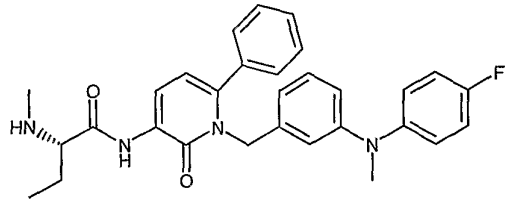
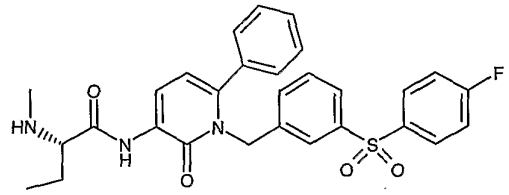
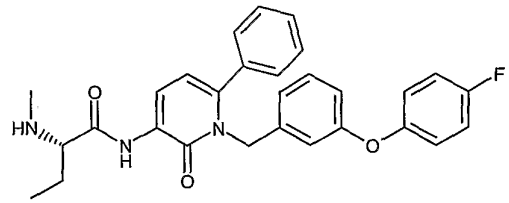
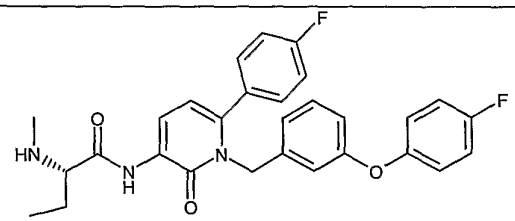
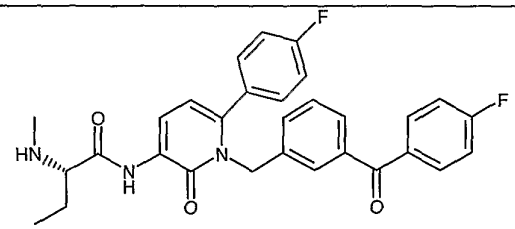
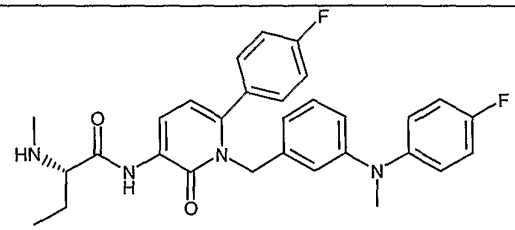
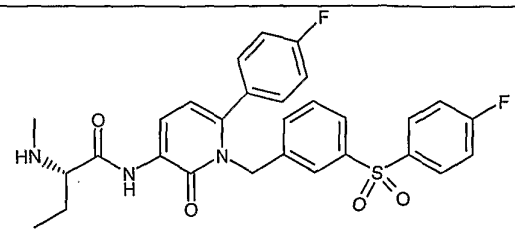
Compound Structure	Example Number
	Example 93 MS 450.3 $(M+H)^+$
	Example 94 MS 428.3 $(M+H)^+$
	Example 95 MS 464.3 $(M+H)^+$
	Example 96 MS 468.3 $(M+H)^+$
	Example 97 MS 400.3 $(M+H)^+$
	Example 98 MS 436.2 $(M+H)^+$
	Example 99 MS 434.2 $(M+H)^+$

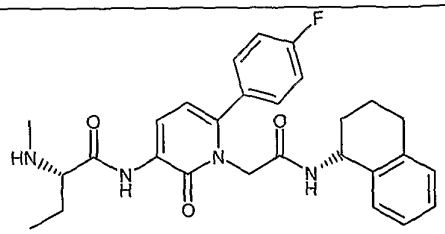
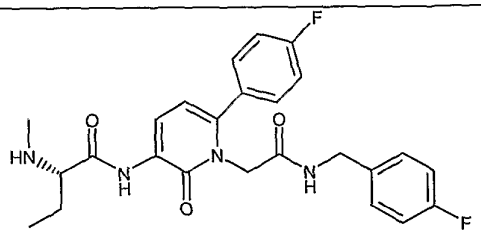
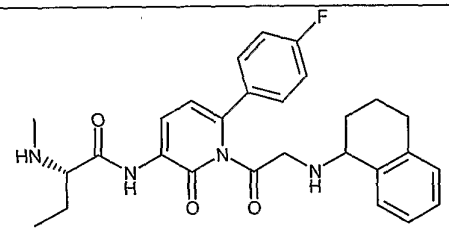
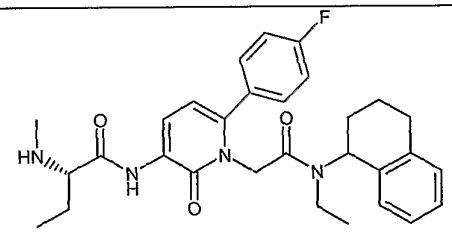
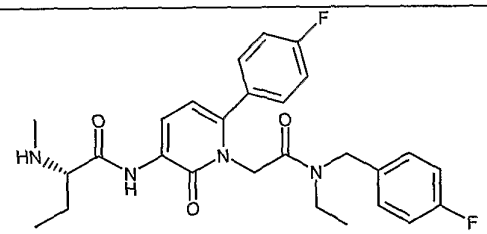
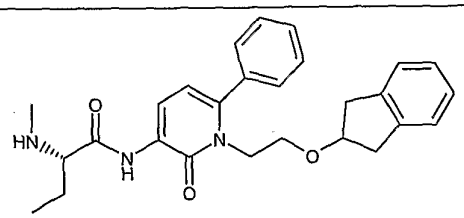
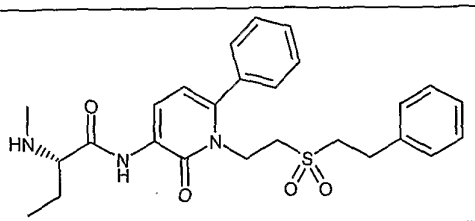
Compound Structure	Example Number
	Example 100 MS 430.3 $(M+H)^+$
	Example 101 MS 450.2 $(M+H)^+$
	Example 102 MS 404.2 $(M+H)^+$
	Example 103 MS 422.2 $(M+H)^+$
	Example 104 MS 448.3 $(M+H)^+$
	Example 105 MS 418.2 $(M+H)^+$
	Example 106 MS 436.3 $(M+H)^+$
	Example 107 MS 420.2 $(M+H)^+$

Compound Structure	Example Number
	Example108 MS 440.2 $(M+H)^+$
	Example 109 MS 434.2 $(M+H)^+$
	Example 110 MS 454.2 $(M+H)^+$
	Example 111 MS 386.2 $(M+H)^+$
	Example 112 MS 422.2 $(M+H)^+$
	Example 113 MS 390.2 $(M+H)^+$
	Example 114 MS 406.2 $(M+H)^+$
	Example 115 MS 408.2 $(M+H)^+$

Compound Structure	Example Number
	Example 116 MS 426.2 $(M+H)^+$
	Example 117 MS 420.2 $(M+H)^+$
	Example 118 MS 434.2 $(M+H)^+$
	Example 119 MS 400.2 $(M+H)^+$
	Example 120 MS 404.2 $(M+H)^+$
	Example 121 MS 420.2 $(M+H)^+$
	Example 122 MS 436.2 $(M+H)^+$
	Example 123 MS 422.2 $(M+H)^+$

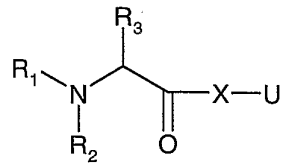
Compound Structure	Example Number
	Example 124 MS 440.2 $(M+H)^+$
	Example 125 MS 427.2 $(M+H)^+$
	Example 126 MS ESI 430.2 $(M+H)^+$
	Example 127 MS ESI 444.2 $(M+H)^+$
	Example 128 MS ESI 498.3 $(M+H)^+$
	Example 129 MS ESI 512.3 $(M+H)^+$
	Example 130 MS ESI 485.3 $(M+H)^+$

Compound Structure	Example Number
	Example 131 MS ESI 499.3 $(M+H)^+$
	Example 132 MS ESI 534.3 $(M+H)^+$
	Example 133 MS ESI 486.3 $(M+H)^+$
	Example 134 MS ESI 414.3 $(M+H)^+$
	Example 135 MS ESI 516.9 $(M+H)^+$
	Example 136 MS ESI 517.3 $(M+H)^+$
	Example 137 MS ESI 552.3 $(M+H)^+$

Compound Structure	Example Number
	Example 138 MS ESI 491.3 $(M+H)^+$
	Example 139 MS ESI 469.3 $(M+H)^+$
	Example 140 MS ESI 491.3 $(M+H)^+$
	Example 141 MS ESI 519.4 $(M+H)^+$
	Example 142 MS ESI 497.3 $(M+H)^+$
	Example 143 MS ESI 446.3 $(M+H)^+$
	Example 144 MS ESI 482.3 $(M+H)^+$

We claim:

1. A compound of the formula (I):



(I)

wherein

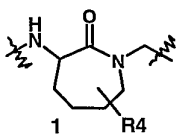
R_1 is H or C_1-C_4 alkyl;

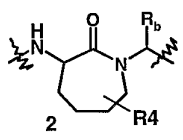
R_2 is H, or C_1-C_4 alkyl which is unsubstituted or substituted by one or more substituents selected from halogen, -OH, -SH, $-OCH_3$, $-SCH_3$, -CN, -SCN and nitro;

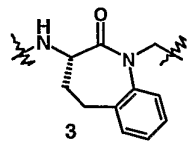
R_3 is H, C_1-C_4 alkyl, $-CF_3$, $-C_2F_5$, $-CH_2$-Z or R_2 and R_3 together form with the nitrogen form a C_3-C_6 heteroaliphatic ring;

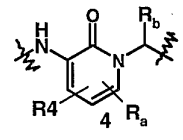
Z is H, -OH, F, Cl, $-CH_3$; $-CF_3$, $-CH_2Cl$, $-CH_2F$ or $-CH_2OH$;

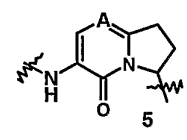
X is a monocyclic or a bicyclic structure selected from the group consisting of:

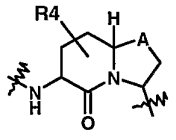

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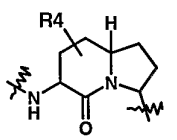

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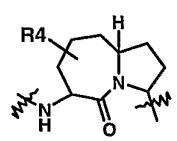

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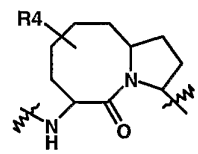

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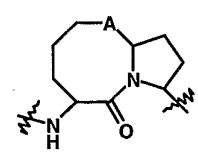

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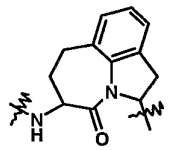

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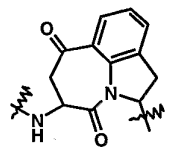

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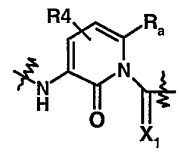

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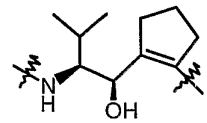

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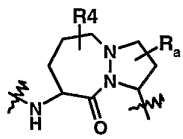

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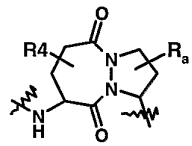

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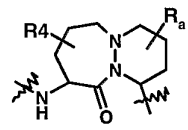

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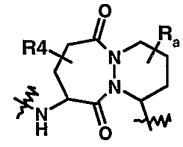

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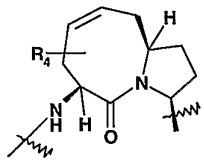

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19

where

A is $-CH_2$, -CH-, N, O, or S;

X_1 is O, S, or NR_a;

R_4, R_a and R_b are independently, H; C_1-C_{16} straight or branched alkyl; C_1-C_{16} alkenyl; C_1-C_{16} alkynyl; or C_1-C_{16} cycloalkyl; -$(CH_2)_{0-6}$-phenyl; $(CH_2)_{0-6}$-het; -O-C_1-C_{16} straight or branched alkyl, -S-C_1-C_{16} straight or branched alkyl; -N-C_1-C_{16} straight or branched alkyl; - -O-C_1-C_{16} alkenyl; -S-C_1-C_{16} alkenyl; -N-C_1-C_{16} alkenyl -O-C_1-C_{16} cycloalkyl; -N-C_1-C_{16} cycloalkyl; -S-C_1-C_{16} cycloalkyl; -O-$(CH_2)_{0-6}$-phenyl; -N-$(CH_2)_{0-6}$-phenyl; -S-$(CH_2)_{0-6}$-phenyl; -O-$(CH_2)_{0-6}$-het; -N-$(CH_2)_{0-6}$-het or -S-$(CH_2)_{0-6}$-het wherein alkyl, cycloalkyl and phenyl are unsubstituted or substituted; or R_4 and R_a may form a ring;

U is -R_5; -CH(R_5)(R_6); -CO-N(R_5)(R_6); -CO-O(R_5); -CO-S(R_5); -CS-N(R_5)(R_6); -N(R_5)-CO-N(R_5)(R_6); -C_1-C_5 alkyl-N(R_5)(R_6);-C_1-C_5-alkyl-O(R_6) or or -C_1-C_5 alkyl-S(O)$_n$(R_6) where n is 0, 1 or 2;

R_5 is H; C_1-C_{10} alkyl; C_3-C_7 cycloalkyl; -$(CH_2)_{1-6}$-C_3-C_7 cycloalkyl; -C_1-C_{10} alkyl-aryl; -$(CH_2)_{0-6}$-phenyl; -$(CH_2)_{0-6}$-C_3-C_7 cycloalkyl-$(CH_2)_{0-6}$-phenyl; -$(CH_2)_{0-4}$CH-$((CH_2)_{1-4}$-phenyl$)_2$; -$(CH_2)_{0-6}$-CH(phenyl)$_2$; -C(O)-C_1-C_{10} alkyl; -C(O)-$(CH_2)_{1-6}$-C_3-C_7 cycloalkyl; -C(O)-$(CH_2)_{0-6}$-phenyl; -$(CH_2)_{1-6}$-het; -C(O)-$(CH_2)_{1-6}$-het; -$(CR_7R_8)_{0-2}$-Aryl-V-Aryl; $CHR_6C(O)N(R_{12})(R_{13})$; C(O)-NH-$CH(R_{11})(R_{14})$ or R_5 is a residue of an amino acid, wherein the alkyl, cycloalkyl, phenyl and aryl substituents are unsubstituted or substituted;

or when U is -CO-N(R_5)(R_6); -CS-N(R_5)(R_6); -N(R_5)-CO-N(R_5)(R_6); or N(R_5)-CO-N(R_5)(R_6), R_5 and R_6 together with the N atom form an aromatic or alihpatic heterocycle;

R_7 and R_8 are independently H, halogen; C_{1-7} alkyl; -OC_{1-7} alkyl; C_{1-7} cycloalkyl; or -OC_{1-7} cycloalkyl wherein the alkyl, cycloalkyl substituents may be substituted or unsubstituted;

V is R_9; R_{10}; CR_9R_{10}; -C(O)-; C(hal)$_2$; -O-; -N(H)-; N(alkyl); N(aryl); S; SO; or S(O)$_2$;

R_9 and R_{10} are independently H, halogen, C_{1-7} alkyl;-OC_{1-7} alkyl; C_{1-7} cycloalkyl; or -OC_{1-7} cycloalkyl wherein the alkyl, cycloalkyl substituents may be substituted or unsubstituted;

R_6 is H; -C_1-C_{10} alkyl; -OH; -O-C_1-C_{10} alkyl; -$(CH_2)_{0-6}$-C_3-C_7 cycloalkyl; -O-$(CH_2)_{0-6}$-aryl; -$(CH_2)_{0-6}$-aryl; phenyl; -$(CH_2)_{1-6}$-het; -O-$(CH_2)_{1-6}$-het; –N(R_{12})(R_{13}); -CNOR_{12}; -S-R_{12}; -S(O)-R_{12}; -S(O)$_2$-R_{12}; or -S(O)$_2$-N$R_{12}R_{13}$ wherein the alkyl, cycloalkyl and aryl substituents are unsubstituted or substituted;

R_{12} and R_{13} are independently H; C_1-C_{10} alkyl; -$(CH_2)_{0-6}$-C_3-C_7 cycloalkyl; -$(CH_2)_{0-6}$-$(CH)_{0-1}(aryl)_{1-2}$; -C(O)-C_1-C_{10} alkyl; -C(O)-$(CH_2)_{1-6}$-C_3-C_7 cycloalkyl; -C(O)-O-$(CH_2)_{0-6}$-aryl; -C(O)-$(CH_2)_{0-6}$-O-fluorenyl; -C(O)-NH-$(CH_2)_{0-6}$-aryl; -C(O)-$(CH_2)_{0-6}$-aryl; or -C(O)-$(CH_2)_{1-6}$-het, wherein the alkyl, cycloalkyl and aryl substituents are unsubstituted or substituted; or a substituent that facilitates transport of the molecule across a cell membrane, or R_{12} and R_{13} together with the nitrogen are het;

where R_{11} and R_{14} are C_{1-7} alkyl; -$(CH_2)_{0-6}$-phenyl; or amide;

aryl is phenyl, naphthyl, or indanyl which is unsubstituted or substituted;

and pharmaceutically acceptable salts thereof.

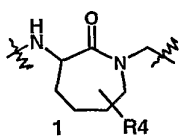
2. A compound of formula (I) according to claim 1 wherein

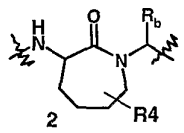
R_1 is H or C_1-C_4 alkyl;

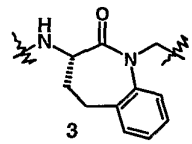
R_2 is H or C_1-C_4 alkyl;

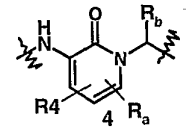
R_3 is H or C_1-C_4 alkyl;

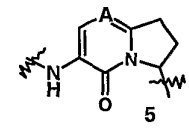
X is a monocyclic or a bicyclic structure selected from the group consisting of:

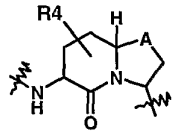

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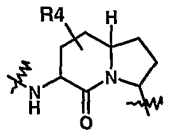

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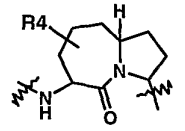

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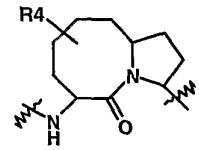

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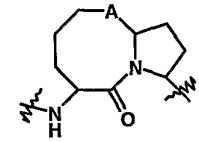

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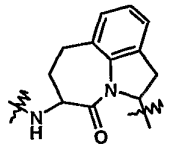

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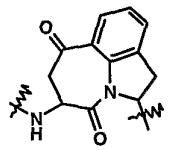

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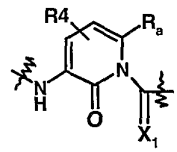

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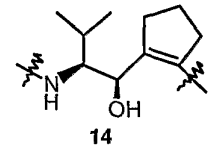

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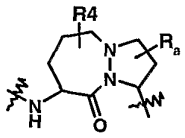

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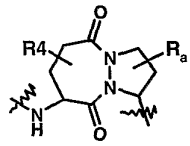

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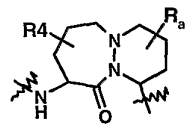

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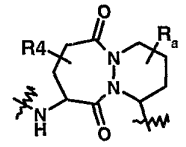

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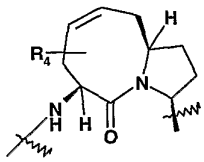

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where

A is $-CH_2$, -CH-, N, O, or S;

X_1 is O, S, or NR_a;

R_4, R_a and R_b are independently, H; C_1-C_{16} straight or branched alkyl; or $-(CH_2)_{0-6}$-phenyl wherein phenyl is unsubstituted with halo;

U is $-R_5$; $-CH(R_5)(R_6)$; C_1-C_5 alkyl-$N(R_5)(R_6)$; or $-CO-N(R_5)(R_6)$;

R_5 is H; C_1-C_{10} alkyl; $-(CH_2)_{0-6}$-phenyl; $-C(O)-C_1-C_{10}$alkyl; $-C(O)-(CH_2)_{0-6}$-phenyl; $-(CR_7R_8)_{0-2}$-Aryl-V-Aryl; $CHR_6C(O)N(R_{12})(R_{13})$; or $C(O)-NH-CH(R_{11})(R_{14})$;

R_7 and R_8 are independently H, halogen; C_{1-7} alkyl; $-OC_{1-7}$ alkyl; C_{1-7} cycloalkyl; or $-OC_{1-7}$ cycloalkyl;

V is -C(O)-; $C(hal)_2$; -O-; -N(H)-; N(alkyl); N(aryl); S; SO; or $S(O)_2$;

R_9 and R_{10} are independently H, halogen, C_{1-7} alkyl;-OC_{1-7} alkyl; C_{1-7} cycloalkyl; or -OC_{1-7} cycloalkyl;

R_6 is H; -C_1-C_{10} alkyl; -OH; -O-C_1-C_{10} alkyl; -$(CH_2)_{0-6}$-phenyl; -$(CH_2)_{0-6}$-aryl-; -O-$(CH_2)_{0-6}$-aryl; phenyl; -$(CH_2)_{1-6}$-het; -O-$(CH_2)_{1-6}$-het; -$N(R_{12})(R_{13})$; -$CNOR_{12}$; -S-R_{12}; -S(O)-R_{12}; -$S(O)_2$-R_{12}; or -$S(O)_2$-$NR_{12}R_{13}$;

R_{12} and R_{13} are independently H, or C_1-C_{10} alkyl;

where R_{11} and R_{14} are C_{1-7} alkyl; -$(CH_2)_{0-6}$-phenyl; or amide;

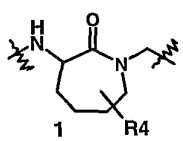
aryl is phenyl, naphthyl, or indanyl which is unsubstituted or substituted;

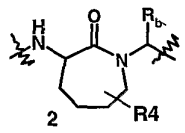
and pharmaceutically acceptable salts thereof.

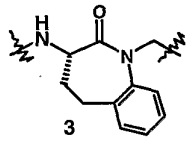
3. A compound of formula (I) according to claim 1 wherein

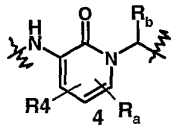
R_1, R_2 and R_3 are independently H or C_1-C_4 alkyl;

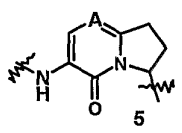
X is a monocyclic or a bicyclic structure selected from the group consisting of:

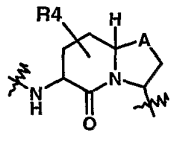

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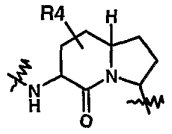

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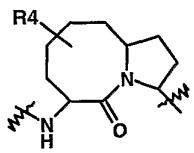

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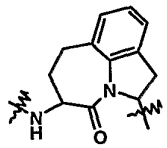

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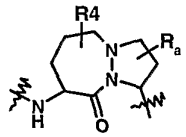

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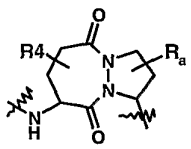

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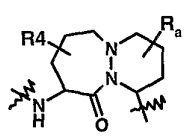

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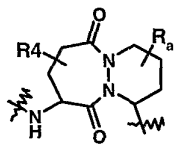

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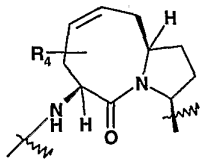

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where

A is -CH_2, -CH-, N, O, or S;

X_1 is O, S, or NR_a;

R_4, R_a and R_b are independently, H; C_1-C_{16} straight or branched alkyl; or -$(CH_2)_{0-6}$-phenyl;

U is -R_5; -CO-N(R_5)(R_6) or C_1-C_5alkyl-NR_6;

R_5 is H; -$(CH_2)_{0-6}$-phenyl; Aryl-V-Aryl; or C(O)-NH-CH(R_{11})(R_{14}) wherein aryl or phenyl may be substituted or unsubstituted;

V is -O-;

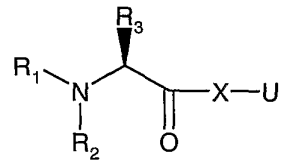
R_6 is H; -C_1-C_{10} alkyl; -OH; -O-C_1-C_{10} alkyl; -O-$(CH_2)_{0-6}$-phenyl; -$(CH_2)_{0-6}$-phenyl; indanyl or phenyl;

where R_{11} and R_{14} are C_{1-7} alkyl; -$(CH_2)_{0-6}$-phenyl; or amide;

aryl is phenyl, naphthyl, or indanyl which is unsubstituted or substituted;

and pharmaceutically acceptable salts thereof.

4. A compound of formula (I) according to Claim 1, having the following stereochemistry:



(II)

5. Use of a compound of formula (I) according to Claim 1 to treat a proliferative disease.

6. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula (I) according to Claim 1.

7. A method of treating a proliferative disease which comprises administering a therapeutically effective amount of a compound of formula (I) according to Claim 1 to a mammal in need of such treatment.

8. A method of Claim 7, wherein the mammal is a human.

9. A process to prepare compound of formula (I) comprising:

(a) coupling of an amine HXU with a t-Boc-L-amino acid or its derivative using peptide coupling agents, such as DCC/HOBt or HBTU/HOBt.

(b) removing t-Boc with trifluoroacetic acid.

10. The process according to Claim 9, wherein the coupling agents are DCC/HOBt or HBTU/HOBt.

11. A compound selected from:

(1S,9S)-9-((S)-2-Methylamino-butyrylamino)-6,10-dioxo-octahydro-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid phenethyl-amide;

(1S,9S)-9-((S)-2-Methylamino-propionylamino)-6,10-dioxo-octahydro-pyridazino[1,2][1,2]diazepine-1-carboxylic acid phenethyl-amide;

(1S,9S)-9-((S)-2-Methylamino-propionylamino)-10-oxo-octahydro-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid phenethyl-amide;

(1S,8S)-8-((S)-2-Methylamino-propionylamino)-9-oxo-hexahydro-pyrazolo[1,2-a][1,2]diazepine-1-carboxylic acid phenethyl-amide;

(1S,8S)-8-((S)-2-Methylamino-butyrylamino)-5,9-dioxo-hexahydro-pyrazolo[1,2-a][1,2]diazepine-1-carboxylic acid phenethyl-amide;

(1S,8S)-8-((S)-2-Methylamino-propionylamino)-5,9-dioxo-hexahydro-pyrazolo[1,2-a][1,2]diazepine-1-carboxylic acid phenethyl-amide;

(1S,8S)-8-((S)-2-Methylamino-butyrylamino)-9-oxo-hexahydro-pyrazolo[1,2-a][1,2]diazepine-1-carboxylic acid phenethyl-amide;

(2S,5S)-5-((S)-2-Methylamino-propionylamino)-4-oxo-1,2,4,5,6,7-hexahydro-azepino[3,2,1-hi]indole-2-carboxylic acid phenethyl-amide;

(3S,6S,8aS)-6-((S)-2-Methylamino-propionylamino)-5-oxo-octahydro-indolizine-3-carboxylic acid phenethyl-amide;

(3R,6S,8aS)-6-((S)-2-Methylamino-propionylamino)-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid phenethyl-amide;

(6S,10aS)-6-((S)-2-Methylamino-propionylamino)-5-oxo-decahydro-pyrrolo[1,2-a]azocine-3-carboxylic acid phenethyl-amide;

(Z)-(3S,6S,10aR)-6-((S)-2-Methylamino-propionylamino)-5-oxo-1,2,3,5,6,7,10,10a-octahydro-pyrrolo[1,2-a]azocine-3-carboxylic acid phenethyl-amide;

(S)-2-Amino-N-{1-[((S)-1-carbamoyl-2-phenyl-ethylcarbamoyl)-methyl]-2-oxo-1,2-dihydro-pyridin-3-yl}-propionamide;

(S)-2-Methylamino-N-[2-oxo-1-(phenethylcarbamoyl-methyl)-1,2-dihydro-pyridin-3-yl]-propionamide;

(S)-2-Methylamino-N-[2-oxo-1-(phenethylcarbamoyl-methyl)-6-phenyl-1,2-dihydro-pyridin-3-yl]-propionamide;

2-Methylamino-N-[6-methyl-2-oxo-1-(phenethylcarbamoyl-methyl)-5-phenyl-1,2-dihydro-pyridin-3-yl]-propionamide;

(S)-N-[6-Butyl-2-oxo-1-(phenethylcarbamoyl-methyl)-1,2-dihydro-pyridin-3-yl]-2-methylamino-propionamide;

2-Methylamino-N-[6-methyl-2-oxo-1-(phenethylcarbamoyl-methyl)-1,2-dihydro-pyridin-3-yl]-propionamide;

(S)-N-[6-Benzyl-2-oxo-1-(phenethylcarbamoyl-methyl)-1,2-dihydro-pyridin-3-yl]-2-methylamino-propionamide;

(S)-2-Methylamino-N-[2-oxo-1-(3-phenoxy-benzyl)-6-phenyl-1,2-dihydro-pyridin-3-yl]-propionamide;

(S)-2-Methylamino-N-[2-oxo-1-(3-phenoxy-benzyl)-1,2-dihydro-pyridin-3-yl]-butyramide;

(S)-6-((S)-2-Methylamino-butyrylamino)-5-oxo-1,2,3,5-tetrahydro-indolizine-3-carboxylic acid phenethyl-amide;

(S)-6-((S)-2-Methylamino-propionylamino)-5-oxo-1,2,3,5-tetrahydro-indolizine-3-carboxylic acid phenethyl-amide;

(S)-6-((S)-2-Methylamino-propionylamino)-5-oxo-1,2,3,5-tetrahydro-indolizine-3-carboxylic acid (2-cyclohexyl-ethyl)-amide;

(S)-2-Methylamino-N-[(S)-2-oxo-1-(phenethylcarbamoyl-methyl)-azepan-3-yl]-propionamide;

2-[(S)-3-((S)-2-Methylamino-propionylamino)-2-oxo-azepan-1-yl]-N-phenethyl-propionamide;

(S)-N-((S)-1-{[2-(2-Methoxy-phenyl)-ethylcarbamoyl]-methyl}-2-oxo-azepan-3-yl)-2-methylamino-propionamine;

(S)-2-Amino-N-{(S)-1-[((S)-1-carbamoyl-2-phenyl-ethylcarbamoyl)-methyl]-2-oxo-azepan-3-yl}-propionamide;

(S)-2-Amino-N-{1-[((S)-1-carbamoyl-2-phenyl-ethylcarbamoyl)-methyl]-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl}-propionamide;

(S)-2-Amino-N-{1-[((S)-1-carbamoyl-2-phenyl-ethylcarbamoyl)-methyl]-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl}-propionamide;

(S)-2-Methylamino-N-[6-methyl-2-oxo-1-(3-phenoxy-benzyl)-1,2-dihydro-pyridin-3-yl]-propionamide;

(S)-2-Methylamino-N-[2-oxo-1-(3-phenoxy-benzyl)-1,2-dihydro-pyridin-3-yl]-propionamide;

(S)-N-[6-Phenyl-2-oxo-1-(3-phenoxy-benzyl)-1,2-dihydro-pyridin-3-yl]-2-methylamino-propionamide;

(Z)-(2S,5S)-5-Ethyl-1-[(S)-2-((S)-2-methylamino-propionylamino)-pentanoyl]-pyrrolidine-2-carboxylic acid phenethyl-amide;

and pharmaceutically acceptable salts thereof.

12. A compound selected from:

(S)-N-{1-[3-(4-Fluoro-benzoyl)-benzyl]-2-oxo-6-phenyl-1,2-dihydro-pyridin-3-yl}-2-ethylamino-ropionamide;

(S)-N-{1-[3-(4-Fluoro-benzoyl)-benzoyl]-2-oxo-6-phenyl-1,2-dihydro-pyridin-3-yl}-2-methylamino-propionamide;

(S)-N-{1-[3-(4-Fluoro-phenylamino)-benzyl]-2-oxo-6-phenyl-1,2-dihydro-pyridin-3-yl}-2-ethylamino-propionamide;

(S)-N-{1-[3-(4-Fluoro-phenylamino)-benzoyl]-2-oxo-6-phenyl-1,2-dihydro-pyridin-3-yl}-2-ethylamino-propionamide;

(S)-N-(1-{3-[(4-Fluoro-phenyl)-methyl-amino]-benzyl}-2-oxo-6-phenyl-1,2-dihydro-pyridin-3-yl)-2-methylamino-propionamide;

(S)-N-(1-{3-[(4-Fluoro-phenyl)-methyl-amino]-benzoyl}-2-oxo-6-phenyl-1,2-dihydro-pyridin-3-yl)-2-methylamino-propionamide;

(S)-N-{1-[3-(4-Fluoro-phenylsulfanyl)-benzyl]-2-oxo-6-phenyl-1,2-dihydro-pyridin-3-yl}-2-methylamino-propionamide;

(S)-N-{1-[3-(4-Fluoro-benzenesulfonyl)-benzyl]-2-oxo-6-phenyl-1,2-dihydro-pyridin-3-yl}-2-methylamino-propionamide;

(S)-N-{1-[3-(4-Fluoro-phenylsulfanyl)-benzoyl]-2-oxo-6-phenyl-1,2-dihydro-pyridin-3-yl}-2-methylamino-propionamide;

(S)-N-{1-[3-(4-Fluoro-benzenesulfonyl)-benzoyl]-2-oxo-6-phenyl-1,2-dihydro-pyridin-3-yl}-2-methylamino-propionamide;

(S)-N-{1-[3-(4-Fluoro-phenoxy)-benzyl]-2-oxo-6-phenyl-1,2-dihydro-pyridin-3-yl}-2-methylamino-propionamide;

(S)-N-{1-[3-(4-Fluoro-phenoxy)-benzoyl]-2-oxo-6-phenyl-1,2-dihydro-pyridin-3-yl}-2-methylamino-propionamide;

(S)-N-[1-[3-(4-Fluoro-phenoxy)-benzyl]-6-(4-fluoro-phenyl)-2-oxo-1,2-dihydro-pyridin-3-yl]-2-methylamino-propionamide;

(S)-N-[1-[3-(4-Fluoro-benzoyl)-benzyl]-6-(4-fluoro-phenyl)-2-oxo-1,2-dihydro-pyridin-3-yl]-2-methylamino-propionamide;

(S)-N-{6-(4-Fluoro-phenyl)-1-[3-(4-fluoro-phenylamino)-benzyl]-2-oxo-1,2-dihydro-pyridin-3-yl}-2-methylamino-propionamide;

(S)-N-(6-(4-Fluoro-phenyl)-1-{3-[(4-fluoro-phenyl)-methyl-amino]-benzyl}-2-oxo-1,2-dihydro-pyridin-3-yl)-2-methylamino-propionamide;

(S)-N-{6-(4-Fluoro-phenyl)-1-[3-(4-fluoro-phenylsulfanyl)-benzyl]-2-oxo-1,2-dihydro-pyridin-3-yl}-2-methylamino-propionamide;

(S)-N-[1-[3-(4-Fluoro-benzenesulfonyl)-benzyl]-6-(4-fluoro-phenyl)-2-oxo-1,2-dihydro-pyridin-3-yl]-2-methylamino-propionamide;

(S)-N-[1-[(2,2-Diphenyl-ethylcarbamoyl)-methyl]-6-(4-fluoro-phenyl)-2-oxo-1,2-dihydro-pyridin-3-yl]-2-methylamino-propionamide;

(S)-N-[1-[(Diphenethylcarbamoyl)-methyl]-6-(4-fluoro-phenyl)-2-oxo-1,2-dihydro-pyridin-3-yl]-2-methylamino-propionamide;

(S)-N-{6-(4-Fluoro-phenyl)-2-oxo-1-[(1,2,3,4-tetrahydro-naphthalen-1-ylcarbamoyl)-methyl]-1,2-dihydro-pyridin-3-yl}-2-methylamino-propionamide;

(S)-2-Methylamino-N-{2-oxo-6-phenyl-1-[(1,2,3,4-tetrahydro-naphthalen-1-ylcarbamoyl)-methyl]-1,2-dihydro-pyridin-3-yl}-propionamide;

(S)-N-{1-[(4-Fluoro-benzylcarbamoyl)-methyl]-2-oxo-6-phenyl-1,2-dihydro-pyridin-3-yl}-2-methylamino-propionamide;

(S)-N-[1-[(4-Fluoro-benzylcarbamoyl)-methyl]-6-(4-fluoro-phenyl)-2-oxo-1,2-dihydro-pyridin-3-yl]-2-methylamino-propionamide;

(S)-N-{6-(4-Fluoro-phenyl)-2-oxo-1-[2-(1,2,3,4-tetrahydro-naphthalen-1-ylamino)-acetyl]-1,2-dihydro-pyridin-3-yl}-2-methylamino-propionamide;

(S)-N-[6-(4-Fluoro-phenyl)-2-oxo-1-(1,2,3,4-tetrahydro-naphthalen-1-ylaminooxalyl)-1,2-dihydro-pyridin-3-yl]-2-methylamino-propionamide;

(S)-N-{6-(4-Fluoro-phenyl)-2-oxo-1-[2-(1,2,3,4-tetrahydro-naphthalen-1-ylamino)-ethyl]-1,2-dihydro-pyridin-3-yl}-2-methylamino-propionamide;

(S)-N-[1-{2-[Ethyl-(1,2,3,4-tetrahydro-naphthalen-1-yl)-amino]-ethyl}-6-(4-fluoro-phenyl)-2-oxo-1,2-dihydro-pyridin-3-yl]-2-methylamino-propionamide;

(S)-N-[1-{[Ethyl-(1,2,3,4-tetrahydro-naphthalen-1-yl)-carbamoyl]-methyl}-6-(4-fluoro-phenyl)-2-oxo-1,2-dihydro-pyridin-3-yl]-2-methylamino-propionamide;

(S)-N-[1-{2-[Ethyl-(1,2,3,4-tetrahydro-naphthalen-1-yl)-amino]-acetyl}-6-(4-fluoro-phenyl)-2-oxo-1,2-dihydro-pyridin-3-yl]-2-methylamino-propionamide;

(S)-N-[1-{[Ethyl-(4-fluoro-benzyl)-carbamoyl]-methyl}-6-(4-fluoro-phenyl)-2-oxo-1,2-dihydro-pyridin-3-yl]-2-methylamino-propionamide;

(S)-N-[1-{2-[Ethyl-(4-fluoro-benzyl)-amino]-ethyl}-6-(4-fluoro-phenyl)-2-oxo-1,2-dihydro-pyridin-3-yl]-2-methylamino-propionamide;

(S)-N-{1-[2-(Indan-2-yloxy)-ethyl]-2-oxo-6-phenyl-1,2-dihydro-pyridin-3-yl}-2-methylamino-propionamide;

(S)-2-Methylamino-N-[2-oxo-1-(2-phenethylsulfanyl-ethyl)-6-phenyl-1,2-dihydro-pyridin-3-yl]-propionamide;

(S)-2-Methylamino-N-{2-oxo-6-phenyl-1-[2-(2-phenyl-ethanesulfonyl)-ethyl]-1,2-dihydro-pyridin-3-yl}-propionamide;

(S)-2-Methylamino-N-[2-oxo-6-phenyl-1-(5-phenyl-pentyl)-1,2-dihydro-pyridin-3-yl]-propionamide;

N-[(4S,7S)-4-(Indan-2-yloxymethyl)-6,10-dioxo-octahydro-pyridazino[1,2-a][1,2]diazepin-7-yl]-2-methylamino-propionamide;

N-((4S,7S)-6,10-Dioxo-4-phenethylsulfanylmethyl-octahydro-pyridazino[1,2-a][1,2]diazepin-7-yl)-2-methylamino-propionamide;

N-[(4S,7S)-6,10-Dioxo-4-(2-phenyl-ethanesulfinylmethyl)-octahydro-pyridazino[1,2-a][1,2]diazepin-7-yl]-2-methylamino-propionamide;

N-[(4S,7S)-6,10-Dioxo-4-(2-phenyl-ethanesulfonylmethyl)-octahydro-pyridazino[1,2-a][1,2]diazepin-7-yl]-2-methylamino-propionamide;

N-[(4S,7S)-6,10-Dioxo-4-(3-phenoxy-phenyl)-octahydro-pyridazino[1,2-a][1,2]diazepin-7-yl]-2-methylamino-propionamide;

N-{(4S,7S)-4-[3-(4-Fluoro-phenoxy)-phenyl]-6,10-dioxo-octahydro-pyridazino[1,2-a][1,2]diazepin-7-yl}-2-methylamino-propionamide;

N-[(4S,7S)-4-(3-Benzoyl-phenyl)-6,10-dioxo-octahydro-pyridazino[1,2-a][1,2]diazepin-7-yl]-2-methylamino-propionamide;

N-[(4S,7S)-4-(3-Benzoyl-phenyl)-6,10-dioxo-octahydro-pyridazino[1,2-a][1,2]diazepin-7-yl]-2-methylamino-butyramide;

N-[(4S,7S)-4-(Indan-2-yloxymethyl)-6,10-dioxo-octahydro-pyridazino[1,2-a][1,2]diazepin-7-yl]-2-methylamino-butyramide;

N-((4S,7S)-6,10-Dioxo-4-phenethylsulfanylmethyl-octahydro-pyridazino[1,2-a][1,2]diazepin-7-yl)-2-methylamino-butyramide;

N-[(4S,7S)-6,10-Dioxo-4-(2-phenyl-ethanesulfinylmethyl)-octahydro-pyridazino[1,2-a][1,2]diazepin-7-yl]-2-methylamino-butyramide;

N-[(4S,7S)-6,10-Dioxo-4-(2-phenyl-ethanesulfonylmethyl)-octahydro-pyridazino[1,2-a][1,2]diazepin-7-yl]-2-methylamino-butyramide;

N-[(4S,7S)-6,10-Dioxo-4-(3-phenoxy-phenyl)-octahydro-pyridazino[1,2-a][1,2]diazepin-7-yl]-2-methylamino-butyramide;

N-{(4S,7S)-4-[3-(4-Fluoro-phenoxy)-phenyl]-6,10-dioxo-octahydro-pyridazino[1,2-a][1,2]diazepin-7-yl}-2-methylamino-butyramide;

N-[(3S,6S,10aS)-3-(Indan-2-yloxymethyl)-5-oxo-decahydro-pyrrolo[1,2-a]azocin-6-yl]-2-methylamino-propionamide;

2-Methylamino-N-((3S,6S,10aS)-5-oxo-3-phenethylsulfanylmethyl-decahydro-pyrrolo[1,2-a]azocin-6-yl)-propionamide;

2-Methylamino-N-[(3S,6S,10aS)-5-oxo-3-(2-phenyl-ethanesulfinylmethyl)-decahydro-pyrrolo[1,2-a]azocin-6-yl]-propionamide;

2-Methylamino-N-[(3S,6S,10aS)-5-oxo-3-(2-phenyl-ethanesulfonylmethyl)-decahydro-pyrrolo[1,2-a]azocin-6-yl]-propionamide;

2-Methylamino-N-[(3S,6S,10aS)-5-oxo-3-(3-phenoxy-phenyl)-decahydro-pyrrolo[1,2-a]azocin-6-yl]-propionamide;

N-{(3S,6S,10aS)-3-[3-(4-Fluoro-phenoxy)-phenyl]-5-oxo-decahydro-pyrrolo[1,2-a]azocin-6-yl}-2-methylamino-propionamide;

N-[(3S,6S,10aS)-3-(3-Benzoyl-phenyl)-5-oxo-decahydro-pyrrolo[1,2-a]azocin-6-yl]-2-methylamino-propionamide;

N-[(3S,6S,10aS)-3-(3-Benzoyl-phenyl)-5-oxo-decahydro-pyrrolo[1,2-a]azocin-6-yl]-2-methylamino-butyramide;

2-Methylamino-N-[(3S,6S,10aS)-5-oxo-3-(2-phenyl-ethanesulfonylmethyl)-decahydro-pyrrolo[1,2-a]azocin-6-yl]-butyramide;

2-Methylamino-N-((3S,6S,10aS)-5-oxo-3-phenethylsulfanylmethyl-decahydro-pyrrolo[1,2-a]azocin-6-yl)-butyramide

2-Methylamino-N-[(3S,6S,10aS)-5-oxo-3-(3-phenoxy-phenyl)-decahydro-pyrrolo[1,2-a]azocin-6-yl]-butyramide;

N-[(3S,6S,10aS)-3-(Indan-2-yloxymethyl)-5-oxo-decahydro-pyrrolo[1,2-a]azocin-6-yl]-2-methylamino-butyramide;

2-Methylamino-N-{(S)-1-[(2S,5S)-2-(2-phenyl-ethanesulfinylmethyl)-5-propyl-pyrrolidine-1-carbonyl]-propyl}-butyramide;

N-{(3S,6S,10aS)-3-[3-(4-Fluoro-phenoxy)-phenyl]-5-oxo-decahydro-pyrrolo[1,2-a]azocin-6-yl}-2-methylamino-butyramide;

N-[(3S,6S,9aS)-3-(Indan-2-yloxymethyl)-5-oxo-octahydro-pyrrolo[1,2-a]azepin-6-yl]-2-methylamino-propionamide;

2-Methylamino-N-[(3S,6S,9aS)-5-oxo-3-(2-phenyl-ethanesulfonylmethyl)-octahydro-pyrrolo[1,2-a]azepin-6-yl]-propionamide;

N-[(3S,6S,9aS)-3-(3-Benzoyl-phenyl)-5-oxo-octahydro-pyrrolo[1,2-a]azepin-6-yl]-2-methylamino-propionamide;

2-Methylamino-N-{(3S,6S,9aS)-5-oxo-3-[3-((Z)-propenyl)-4-vinyl-cyclopent-3-enyloxymethyl]-octahydro-pyrrolo[1,2-a]azepin-6-yl}-butyramide;

2-Methylamino-N-[(3S,6S,9aS)-5-oxo-3-(2-phenyl-ethanesulfonylmethyl)-octahydro-pyrrolo[1,2-a]azepin-6-yl]-butyramide;

2-Methylamino-N-((3S,6S,9aS)-5-oxo-3-phenethylsulfanylmethyl-octahydro-pyrrolo[1,2-a]azepin-6-yl)-propionamide;

2-Methylamino-N-[(3S,6S,9aS)-5-oxo-3-(3-phenoxy-phenyl)-octahydro-pyrrolo[1,2-a]azepin-6-yl]-propionamide;

N-[(3S,6S,9aS)-3-(3-Benzoyl-phenyl)-5-oxo-octahydro-pyrrolo[1,2-a]azepin-6-yl]-2-methylamino-butyramide;

2-Methylamino-N-((3S,6S,9aS)-5-oxo-3-henethylsulfanylmethyl-octahydro-pyrrolo[1,2-a]azepin-6-yl)-butyramide;

2-Methylamino-N-[(3S,6S,9aS)-5-oxo-3-(3-phenoxy-phenyl)-octahydro-pyrrolo[1,2-a]azepin-6-yl]-butyramide;

2-Methylamino-N-[(3S,6S,9aS)-5-oxo-3-(2-phenyl-ethanesulfinylmethyl)-octahydro-pyrrolo[1,2-a]azepin-6-yl]-propionamide;

N-{(3S,6S,9aS)-3-[3-(4-Fluoro-phenoxy)-phenyl]-5-oxo-octahydro-pyrrolo[1,2-a]azepin-6-yl}-2-methylamino-propionamide;

2-Methylamino-N-[(3S,6S,9aS)-5-oxo-3-(2-phenyl-ethanesulfinylmethyl)-octahydro-pyrrolo[1,2-a]azepin-6-yl]-butyramide;

N-{(3S,6S,9aS)-3-[3-(4-Fluoro-phenoxy)-phenyl]-5-oxo-octahydro-pyrrolo[1,2-a]azepin-6-yl}-2-methylamino-butyramide;

N-[(3S,6S,8aS)-3-(Indan-2-yloxymethyl)-5-oxo-octahydro-indolizin-6-yl]-2-methylamino-propionamide;

2-Methylamino-N-[(3S,6S,8aS)-5-oxo-3-(2-phenyl-ethanesulfonylmethyl)-octahydro-indolizin-6-yl]-propionamide;

2-Methylamino-N-((3S,6S,8aS)-5-oxo-3-phenethylsulfanylmethyl-octahydro-indolizin-6-yl)-propionamide;

2-Methylamino-N-[(3S,6S,8aS)-5-oxo-3-(2-phenyl-ethanesulfinylmethyl)-octahydro-indolizin-6-yl]-propionamide;

2-Methylamino-N-[(3S,6S,8aS)-5-oxo-3-(3-phenoxy-phenyl)-octahydro-indolizin-6-yl]-propionamide;

N-{(3S,6S,8aS)-3-[3-(4-Fluoro-phenoxy)-phenyl]-5-oxo-octahydro-indolizin-6-yl}-2-methylamino-propionamide;

N-[(3S,6S,8aS)-3-(3-Benzoyl-phenyl)-5-oxo-octahydro-indolizin-6-yl]-2-methylamino-propionamide;

N-[(3S,6S,8aS)-3-(3-Benzoyl-phenyl)-5-oxo-octahydro-indolizin-6-yl]-2-methylamino-butyramide;

N-[(3S,6S,8aS)-3-(Indan-2-yloxymethyl)-5-oxo-octahydro-indolizin-6-yl]-2-methylamino-butyramide;

2-Methylamino-N-((3S,6S,8aS)-5-oxo-3-phenethylsulfanylmethyl-octahydro-indolizin-6-yl)-butyramide;

2-Methylamino-N-[(3S,6S,8aS)-5-oxo-3-(2-phenyl-ethanesulfinylmethyl)-octahydro-indolizin-6-yl]-butyramide;

2-Methylamino-N-[(3S,6S,8aS)-5-oxo-3-(2-phenyl-ethanesulfonylmethyl)-octahydro-indolizin-6-yl]-butyramide;

2-Methylamino-N-[(3S,6S,8aS)-5-oxo-3-(3-phenoxy-phenyl)-octahydro-indolizin-6-yl]-butyramide;

N-{(3S,6S,8aS)-3-[3-(4-Fluoro-phenoxy)-phenyl]-5-oxo-octahydro-indolizin-6-yl}-2-methylamino-butyramide;

(S)-N-{1-[2-(1,3-Dihydro-isoindol-2-yl)-2-oxo-ethyl]-2-oxo-6-phenyl-1,2-dihydro-pyridin-3-yl}-2-methylamino-propionamide;

(S)-N-{1-[2-(1,3-Dihydro-isoindol-2-yl)-2-oxo-ethyl]-2-oxo-6-phenyl-1,2-dihydro-pyridin-3-yl}-2-methylamino- butyramide;

(S)-N-{1-[3-(4-Fluoro-benzoyl)-benzyl]-2-oxo-6-phenyl-1,2-dihydro-pyridin-3-yl}-2-methylamino-butyramide;

(S)-N-{1-[3-(4-Fluoro-benzoyl)-benzoyl]-2-oxo-6-phenyl-1,2-dihydro-pyridin-3-yl}-2-methylamino- butyramide;

(S)-N-{1-[3-(4-Fluoro-phenylamino)-benzyl]-2-oxo-6-phenyl-1,2-dihydro-pyridin-3-yl}-2-methylamino- butyramide;

(S)-N-(1-{3-[(4-Fluoro-phenyl)-methyl-amino]-benzyl}-2-oxo-6-phenyl-1,2-dihydro-pyridin-3-yl)-2-methylamino- butyramide;

(S)-N-{1-[3-(4-Fluoro-benzenesulfonyl)-benzyl]-2-oxo-6-phenyl-1,2-dihydro-pyridin-3-yl}-2-methylamino- butyramide;

(S)-N-{1-[3-(4-Fluoro-phenoxy)-benzyl]-2-oxo-6-phenyl-1,2-dihydro-pyridin-3-yl}-2-methylamino- butyramide;

(S)-N-[1-[3-(4-Fluoro-phenoxy)-benzyl]-6-(4-fluoro-phenyl)-2-oxo-1,2-dihydro-pyridin-3-yl]-2-methylamino-butyramide;

(S)-N-[1-[3-(4-Fluoro-benzoyl)-benzyl]-6-(4-fluoro-phenyl)-2-oxo-1,2-dihydro-pyridin-3-yl]-2-methylamino-butyramide;

(S)-N-(6-(4-Fluoro-phenyl)-1-{3-[(4-fluoro-phenyl)-methyl-amino]-benzyl}-2-oxo-1,2-dihydro-pyridin-3-yl)-2-methylamino- butyramide;

(S)-N-[1-[3-(4-Fluoro-benzenesulfonyl)-benzyl]-6-(4-fluoro-phenyl)-2-oxo-1,2-dihydro-pyridin-3-yl]-2-methylamino- butyramide;

(S)-N-{6-(4-Fluoro-phenyl)-2-oxo-1-[(1,2,3,4-tetrahydro-naphthalen-1-ylcarbamoyl)-methyl]-1,2-dihydro-pyridin-3-yl}-2-methylamino-butyramide;

(S)-N-[1-[(4-Fluoro-benzylcarbamoyl)-methyl]-6-(4-fluoro-phenyl)-2-oxo-1,2-dihydro-pyridin-3-yl]-2-methylamino-butyramide;

(S)-N-{6-(4-Fluoro-phenyl)-2-oxo-1-[2-(1,2,3,4-tetrahydro-naphthalen-1-ylamino)-acetyl]-1,2-dihydro-pyridin-3-yl}-2-methylamino-butyramide;

(S)-N-[1-{[Ethyl-(1,2,3,4-tetrahydro-naphthalen-1-yl)-carbamoyl]-methyl}-6-(4-fluoro-phenyl)-2-oxo-1,2-dihydro-pyridin-3-yl]-2-methylamino-butyramide;

(S)-N-[1-{[Ethyl-(4-fluoro-benzyl)-carbamoyl]-methyl}-6-(4-fluoro-phenyl)-2-oxo-1,2-dihydro-pyridin-3-yl]-2-methylamino-butyramide;

(S)-N-{1-[2-(Indan-2-yloxy)-ethyl]-2-oxo-6-phenyl-1,2-dihydro-pyridin-3-yl}-2-methylamino-butyramide;

(S)-2-Methylamino-N-{2-oxo-6-phenyl-1-[2-(2-phenyl-ethanesulfonyl)-ethyl]-1,2-dihydro-pyridin-3-yl}-butyramide;

and pharmaceutically acceptable salts thereof.